Crohn's Disease and Ulcerative Colitis Pricing and Reimbursement

Disease Pricing and Reimbursement / Immunology and Inflammation

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CONTENTS

Published on 16 March 2018

Published on 16 March 2018

OVERVIEW

Payers view spending on inflammatory bowel disease (IBD) drugs as significant, as there is a large patient base requiring expensive biologic therapies. The market has been long dominated by the TNF-alpha inhibitors Humira and Remicade, but more recent biologic launches such as Entyvio and Stelara have focused on novel mechanisms of action. Additionally, another alpha integrin, etrolizumab, is a further biologic of interest to clinicians.

The IBD pipeline is also expecting the launches of novel oral agents such as JAK inhibitors Xeljanz and filgotinib, as well as the S1P receptor antagonist ozanimod. Payers fully expect that these pipeline agents will continue to fuel the growth of the IBD market, and that the launches of TNF-alpha inhibitor biosimilars will not do much to temper growth. Consequently, payers have been restricting the prescribing of the non-TNF-alpha inhibitors to later lines of therapy – and after the TNF-alpha inhibitors whenever possible – to ensure biosimilar savings are realized. European payers are enacting national and regional restrictions: using start-and-stop criteria, delineating therapeutic lines, and requiring discounts in exchange for access to earlier lines of treatment. US payers mandate prior authorization, with most payers requiring failures with TNF-alpha inhibitors prior to accessing Entyvio or Stelara.

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EXECUTIVE SUMMARY

Payers are not enthusiastic regarding the launches of oral compounds in IBD

Payers remain largely unimpressed regarding the launches of new oral compounds in ulcerative colitis (UC) and Crohn's disease (CD), as the drugs are not more efficacious than current gold-standard TNF-alpha inhibitors, and have the potential to increase total treatment costs. Additionally, payers are split with regard to the therapeutic placement of these compounds, with some believing that the drugs will be relegated to later lines only when other biologic therapies have failed, while others think that placement as a bridge between conventional therapies and biologics is possible, but only at a significantly lower price than biologics. Payers are in agreement that in either case, the oral compounds will most likely serve smaller patient subgroups.

Stelara's faster onset of action during the induction phase gives it an advantage over Entyvio in CD

Stelara's (ustekinumab; Johnson & Johnson/Mitsubishi Tanabe) faster onset of action, which is seen during the induction phase, allows physicians to delineate quickly between responders and non-responders, providing an advantage over Entyvio (vedolizumab; Takeda). The practice could further advantage Stelara, especially as Johnson & Johnson has agreed to provide intravenous dosing at a reduced price in some markets. The interleukin-12/23 inhibitor could be further boosted provided that its overall cost during the maintenance phase is less than that of Entyvio.

Without head-to-head trials, oral compounds are unlikely to achieve differentiation and must compete on price

Oral compounds for IBD are absent from head-to-head trials either among one other or with TNF-alpha inhibitors. Without such trials, payers expect differentiation between Xeljanz (tofacitinib; Pfizer), ozanimod (Celgene), and filgotinib (Galapagos/Gilead) to be very difficult. Manufacturers will likely need to concede on price in order to attain placement of their new drugs in the pathway, as a lower price can mean greater access to patients in earlier lines.

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REGULATORY LABELS

MARKETED CROHN'S DISEASE PRODUCTS IN THE US, JAPAN, AND FIVE MAJOR EU MARKETS

Table 1: **Marketed products and approved indications for Crohn's disease drugs in the US, Japan, and five major EU markets**

Drug	Class	EU	US	Japan	Regimens and duration
Cimzia	TNF-alpha MAb	n/a (not approved)	Reduces signs and symptoms and maintains clinical response for adults with moderate to severe active CD with inadequate response to conventional therapy. Cimzia has a black box warning for TB, invasive fungal, and other opportunistic infections with fatality. Test for TB is required, and therapy for TB should be initiated in positive tests. All patients should be monitored for TB during treatment	n/a (not approved)	SC: 400mg at weeks 0, 2, and 4, then 400mg every four weeks
Entyvio	MAb against alpha-4-beta-7 integrin receptor	Adults with moderate to severe active CD who are intolerant to or have had an inadequate response with conventional therapy or a TNF-alpha inhibitor	Achieve clinical response and clinical remission, and achieve CS-free remission for adults with moderate to active CD with intolerance, inadequate response, or loss of response to a TNF-alpha inhibitor or immunomodulator; or if patient is intolerant to or had inadequate response with or demonstrated dependence on CSs	n/a (not approved)	IV: 300mg at weeks 0, 2, and 6, then every eight weeks

Table 1: **Marketed products and approved indications for Crohn's disease drugs in the US, Japan, and five major EU markets**

Humira	TNF-alpha MAb	Adults with moderate to severe active CD who are contraindicated or intolerant or have not responded despite a full and adequate course of therapy with a CS and/or an immunosuppressant. Children and adolescents (at least six years old) with moderate to severe active CD who are intolerant, contraindicated, or have had an inadequate response to conventional therapy including primary nutrition therapy and a CS and/or an immunomodulator	Reduces signs and symptoms and induces and maintains clinical remission for adults with moderate to severe active CD with inadequate response to conventional therapy. Humira also reduces signs and symptoms and induces clinical remission in patients who no longer respond to or are intolerant to infliximab. Reduces signs and symptoms and induces and maintains clinical remission in patients with moderate to severe active CD in children (at least six years old) with inadequate response to CSs or immunomodulators such as AZA, 6-MP, or MTX. Humira has a black box warning for serious infections and malignancy	Induces remission and maintenance therapy for moderate to severe active CD in patients who have not sufficiently responded to conventional treatment	SC: Adults and pediatric patients (weighing at least 40kg): Day 1: 160mg; Day 15: 80mg; Day 29 onwards: Maintenance dose of 40mg every other week Pediatric patients (weighing 17–40kg): Day 1: 80mg; Day 15: 40mg; Day 29 onwards: Maintenance dose of 20mg every other week
Remicade	TNF-alpha MAb	Adults with moderate to severe active CD, contraindicated or intolerant or have not responded to a full and adequate course of therapy with CSs and/or an immunosuppressant. Adults with fistulizing active CD who have not responded despite a full and adequate course of therapy with conventional treatment (antibiotics, drainage, and immunosuppressive therapy). Children (aged 6–17 years) with severe active CD, who are intolerant, contraindicated, or have not responded to conventional therapy including a CS, an immunomodulator, and primary nutrition therapy	Reduces signs and symptoms and induces and maintains clinical response in adults and children (at least six years old) with moderate to severe active CD with inadequate response to conventional therapy. In adults, also reduces the number of draining enterocutaneous and rectovaginal fistulas, and maintains fistula closure in patients with fistulizing CD	Maintenance therapy in CD (orphan drug)	IV: 5mg/kg at weeks 0, 2, and 6, then every eight weeks (adult and pediatric), increase dose to 10mg/kg in adult patients who lose response

Table 1: **Marketed products and approved indications for Crohn's disease drugs in the US, Japan, and five major EU markets**

Stelara	IL-12/23 MAb	Adults with moderate to severe active CD with inadequate response, loss of response, or who were intolerant or contraindicated to either conventional therapy or TNF-alpha inhibitor	Adults with moderate to severe active CD who have failed or were intolerant to treatment with immunomodulators or CSs, but who have never failed a TNF-alpha inhibitor, or intolerant, or failed with TNF-alpha inhibitor	Induction and maintenance therapy for moderate to severe active CD in patients who have not sufficiently responded to conventional treatments	IV: Initial dosage: Patients weighing ≤55kg: 260mg; >55kg to 85kg: 390mg; >85kg = 520mg, followed by SC maintenance dose of 90mg every eight weeks
Tysabri	MAb against alpha-integrin	n/a (not approved)	Induce and maintain clinical response and remission in adults with moderate to severe active CD with evidence of inflammation who have had an inadequate response or are intolerant to conventional therapy and TNF-alpha inhibitor. Tysabri has a black box warning for PML, and is only available through restricted TOUCH prescribing distribution program	n/a (not approved)	IV: 300mg once monthly

6-MP = mercaptopurine; AZA = azathioprine; CD = Crohn's disease; CS = corticosteroid; IL = interleukin; IV = intravenous; MAb = monoclonal antibody; MTX = methotrexate; PML = progressive multifocal leukoencephalopathy; SC = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor

Source: EMA, 2008; 2009; 2013; 2014a; FDA, 2014; 2015a; 2017a/b/c/d

MARKETED ULCERATIVE COLITIS PRODUCTS IN THE US, JAPAN, AND FIVE MAJOR EU MARKETS

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Table 2: **Marketed products and approved indications for ulcerative colitis drugs in the US, Japan, and five major EU markets**

Drug	Class	EU	US	Japan	Regimens and duration
Entyvio	MAb against alpha-4-beta-7 integrin receptor	Adults with moderate to severe active UC with an inadequate response, contraindication, or intolerance to conventional therapy or a TNF-alpha inhibitor	Induce and maintain clinical remission and clinical response, improve endoscopic appearance of the mucosa, and achieve CS-free remission for adults with moderate to severe active UC with intolerance, inadequate response, or loss of response to a TNF-alpha inhibitor or immunomodulator; or the patient is intolerant to or had inadequate response with or demonstrated dependence on CSs	n/a (not approved)	IV: 300mg at weeks 0, 2, and 6, then every eight weeks
Humira	TNF-alpha MAb	Adults with moderate to severe active UC with inadequate response, contraindication, or intolerance to conventional therapy including CSs and 6-MP or AZA	Induce and sustain clinical remission in adults with moderate to severe active UC with inadequate response to immunosuppressants (CS, AZA, or 6-MP). Not established for intolerant patients or for those who have lost response to TNF-alpha inhibitors. Humira has a black box warning for serious infections and malignancy. Only continue in patients who show clinical remission at day 57 of therapy	Patients with moderate to severe UC who have not responded sufficiently to conventional treatments	SC: 160mg on day 1, followed by 80mg on day 15. On day 29, begin maintenance dose of 40mg every other week

Table 2: **Marketed products and approved indications for ulcerative colitis drugs in the US, Japan, and five major EU markets**

Remicade	TNF-alpha MAb	Adults with moderate to severe active UC with an inadequate response, contraindication, or intolerance to conventional therapy including CSs and 6-MP or AZA. Children and adolescents (aged 6–17 years) with severe active UC with an inadequate response, contraindication, or intolerance to conventional therapy including CSs and 6-MP or AZA	Reduce signs and symptoms and induce and maintain clinical response in adults and children (at least six years old) with moderate to severe active UC with inadequate response to conventional therapy. In adults, also maintains mucosal healing and eliminates use of CSs	Patients with moderate to severe UC who have not responded sufficiently to conventional treatments	5mg/kg at 0, 2, and 6 weeks, then every eight weeks
Simponi	TNF-alpha MAb	Adults with moderate to severe active UC with an inadequate response, intolerance, or contraindication to conventional therapy including CSs and 6-MP or AZA	Induce and maintain clinical response, induce clinical remission, achieve and sustain clinical remission in induction responders, and improve endoscopic appearance of mucosa during induction therapy for adults with moderate to severe UC with an inadequate response or intolerant to prior treatment or requiring continuous steroid therapy	Improve and maintain patients with moderate to severe UC who have not responded sufficiently to conventional treatments	SC: 200mg at week 0, then 100mg at week 2, then 100mg every four weeks

6-MP = mercaptopurine; AZA = azathioprine; CS = corticosteroid; IV = intravenous; MAb = monoclonal antibody; SC = subcutaneous; TNF = tumor necrosis factor; UC = ulcerative colitis

Source: EMA, 2008; 2009; 2014a/b; FDA, 2014; 2015a/b; 2017b; PMDA, 2007; 2010; 2013; 2017

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GLOBAL ACCESS LEVERS AND BARRIERS

INSIGHTS AND STRATEGIC RECOMMENDATIONS

- The budget impact of inflammatory bowel disease (IBD) drugs is large, with much of the spend due to expensive biologic agents. Despite this, within the immunology and inflammation area, the budget impact of IBD is not as high as that of rheumatoid arthritis (RA). Payers expect that the launches of biosimilar tumor necrosis factor (TNF)-alpha inhibitors will temper spending somewhat, but expect that the approvals of new pipeline agents will continue to increase overall spend in IBD.

- Access to IBD medications is restricted at the national and, to some extent, regional level in the US and five major EU markets (France, Germany, Italy, Spain, and the UK). Patients are required to use conventional therapies prior to accessing biologics, unless the drugs are contraindicated or the patient is intolerant to them. TNF-alpha inhibitors are considered as first-line options among biologics even though non-TNF-alpha inhibitors have marketing authorization for use in line with TNF-alpha inhibitors. Some national payers express further restrictions, limiting the use of Entyvio (vedolizumab; Takeda) more so than Stelara (ustekinumab; Johnson & Johnson/Mitsubishi Tanabe) in Crohn's disease (CD).

- IBD drugs fall under the broader immunology and inflammation category, where products are often managed by the molecule or class in all of their approved indications, adding further complexity to managing their cost. Contracting arrangements will need to account for the impact of approvals in other, more prevalent indications.

- Patients with severe ulcerative colitis (UC) and CD and those refractory to available therapies represent the largest unmet need from payers' and physicians' perspectives. Payers will likely be receptive to pipeline drugs aimed towards later-line patients as they could delay surgery for many of those patients with severe disease.

BIOLOGICS COMPRISE THE MAJORITY OF SPEND IN IBD; NEW AGENTS WILL CONTINUE TO INCREASE SPEND

Payers assert that the budget impact of IBD drugs is significant, with most of the spend attributed to biologics. The overall budget is not as high as for other autoimmune and inflammatory indications, such as RA, but expenditure on IBD drugs is nevertheless an ongoing concern as prices for these medications continue to increase, and IBD has a large patient base requiring biologic therapy. Payers hoping to see cost reductions following the launches of biosimilar TNF-alpha inhibitors are concerned that a rich pipeline in IBD will temper the cost savings generated.

"Payers are seeing that the spending is really quite substantial, and especially the spending on biologics for these two indications is quite substantial because there might be let us say 50,000 patients for both conditions who are eligible for a biologic, and almost all of them do receive one because there is strict management at the local level in France, therefore the budget impact is quite substantial. So, the spending per patient is quite substantial, and the number of patients is also substantial."

Former French national payer

"In my opinion it is quite large. It is not the first, but if you take away the oncology drugs and oncology patients, bowel disease is probably the second or third one. First of all, we have rheumatology, and bowel disease is the second or third in cost in terms of budget impact. It is less than rheumatoid arthritis, but in order of diseases it is probably the second or third one."

Spanish local payer

"So, it has been a high priority and a focus for us and primarily that was instigated by the availability of biosimilar infliximab and also NICE positive technology appraisals, which mandate that we have to allow funding for the biologics, so things like vedolizumab that have come through. Ustekinumab came through last week from NICE as a positive FAD [final appraisal determination], so very much a priority because of the biologics and because of the still growing trend. When I look at my graphs on spend in gastro, they are still increasing. As much as [we want the spend] to flatten off; [...] we are still heading for a growth area despite the fact that we have had the biologics for a while now."

UK regional payer

"It is now the number one drug category for both specialty and non-specialty, consuming about 35% of our total specialty budget, a little bit over $100 per member per year. It is the whole category of targeted immunomodulators, but let us face it, it is really three major disease states: psoriasis, inflammatory bowel disease, and the inflammatory arthritis diseases, and out of those RA is about 50%, inflammatory bowel is about 20%, and the dermatologic conditions are the other 30%."

US payer

"Immunodepressant drugs and biological drugs are the third or fourth group in Catalonia in terms of expense or expenditure. It is a growing group with a growth index each year, and I think that the first group is hepatitis C and the second group is immunosuppressants that are growing each year."

Spanish regional payer

"Big concerns, and I think these concerns have come from the historical view of how these drugs got into ulcerative colitis, in that the biologics, the clinicians were using them before they really had licenses in UC. So, what we found is payers were always pushing back while clinicians were trying to use them. Once NICE and the HTA bodies finally gave approval we kind of still pushed back. [...] It is almost like payers decided: 'look, the biologics do not really have value here in this area. They work for rheumatoid, but they are not giving us what we want here,' but nevertheless they are here. So, we are now reimbursing them and we are using biologics for active UC and we are even doing sequential therapy for failure after drugs that have failed, you know, conventional treatments. [...] [We are] less worried because biosimilars are coming [...] because my view is what will happen is the standard of care will become the biosimilar replacements of these original biologics, such as Remicade and Humira and Simponi, and these other drugs coming in with different modes of action, [...] maybe interleukin and other areas, will always be subservient to the TNFs."

UK local payer

"The concerns are pretty high because the price increases on these therapies have been outrageous for the last several years. So, most of the manufacturers have raised price without reasonable justification, so that certainly concerns us. There is not a lot we can do about it, but nonetheless you know."

US payer

"[The spend] will probably increase; the difference between these kinds of patients and rheumatology patients is that these are quite difficult to control. If the illness is severe we have a lot of problems with these kinds of patients, and I suppose with more effective drugs we will increase the budget impact, and increase the cost."

Spanish local payer

"My concern is that [pipeline drugs] are not going to replace, they are actually going to add to the lines of therapy. So, a good model is rheumatoid arthritis [or psoriasis] where some of these drugs have been around previously. For what we can see now is more competition, but

equally there are more options for patients in terms of a third line, a fourth line, and orals versus injectables, so yes, I do not think we are going to replace. I think there are going to be cost pressures and I think I would be a little naïve if I just thought that this is going to replace existing [therapy]."

UK regional payer

"This category is increasing; is it because of new drugs to market or is it because of new patients, or is it because of price increases? And the answer is it is a little bit of all. [...] There are some drugs that have come out or are in the pipeline whose first indication will be GI, and then some of the older drugs are being repurposed and there is going to be a handful of new alpha-integrin inhibitors to compete with natalizumab and others. [...] JAK inhibitors I think are out there for these diseases as well, and you have a number of them. [...] I think we have recognized since the beginning of time drugs are kind of unique, whenever you add a new drug to a category it can grow the entire category, which is kind of mystifying because theoretically you should have the same number of patients, but that is generally not the case. [...] Sometimes I think it is because the new drugs come out at a higher price point and then everybody else follows suit to raise their price."

US payer

"The uptake of infliximab instead of Remicade has shrunk the budget, but the payers do not see that very precisely because the list price is quite high and the confidential discount is not known, so the budget impact is still a concern, and of course vedolizumab is not available as a biosimilar, the same for Stelara that was approved with an ASMR IV in Crohn's disease quite recently."

Former French national payer

"Currently it is mostly to focus on the biosimilars, because for new drugs there is always a problem. We have horizon scanning and yes, we are aware of the number of applications for patents for new drugs, but we do not know the price of the new drug and so we cannot calculate the potential budget impact until the final price is set by the manufacturer. We still have free pricing in the first year and so we mainly focus on the things we can do now, which is the biosimilar uptake."

German sickness funds payer

"The epidemiology of [IBD] is not particularly high in Italy compared to other countries, compared to the US or Canada or even the UK or Spain, Italy has a lower incidence range of these diseases, and my data are indicating that ulcerative colitis is about 6.5 cases per 100,000 people, and Crohn's disease is about 3.8 cases per 100,000 people, so it is not really among the most frequent diseases for the intestinal tract."

Former Italian national payer

PAYERS RESTRICT ACCESS TO IBD MEDICATIONS

Access to IBD medications is restricted in the US and five major EU markets, although the control mechanisms vary by country. In Europe, IBD medications are subject to national evaluations such as technology appraisals by the National Institute for Health and Care Excellence (NICE) or the Scottish Medicines Consortium in the UK, by the Federal Joint Committee (G-BA; Gemeinsamer Bundesausschuss) in Germany, or by the French National Authority for Health (HAS; Haute Autorité de Santé) in France. Moreover, across many of the European countries, regional and local payers also have their say on preferred branded products among the available biologics. In Italy and Spain, regional or local payers can introduce more restrictive access criteria, while in Germany sickness funds set prescribing limits for physicians. Similar restrictions are seen in the US market, where payers, bound by contracting agreements, instate step therapy requirements – usually with Humira (adalimumab; AbbVie/Eisai) – before allowing non-preferred compounds.

Universally, payers require patients to have experienced therapeutic failure with conventional non-biologic therapies such as mercaptopurine (6-MP), azathioprine (AZA), or corticosteroids (CSs), unless contraindicated or intolerant, prior to accessing more expensive medications. TNF-alpha inhibitors remain first-line choices among the available biologic options. Some payers opt for Humira over biosimilar infliximab or Remicade (infliximab; Johnson & Johnson/Mitsubishi Tanabe/Merck & Co) or the second-generation TNF-alpha inhibitors Cimzia (certolizumab pegol; UCB/Astellas) (CD) and Simponi (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) (UC). Others are keen to take advantage of the cost savings of biosimilar infliximab. Interleukin (IL) therapies and integrin class antibodies approved for TNF-alpha inhibitor-naïve patients continue to face restrictions, relegating these therapies to cases of contraindication, intolerance, or failure with TNF-alpha inhibitors. Many key opinion leaders interviewed by Datamonitor Healthcare state, however, that physicians have latitude in prescribing drugs, as long as payer requirements are fulfilled.

"It would be in line with the NICE guidance so patients would start off on acetylcholinesterase inhibitors and then move on to a biologic, either infliximab or adalimumab, and then move to vedolizumab and then potentially surgery. [...] We have had quite a high use locally in my area for vedolizumab, and making sure that we are encouraging use of biosimilar wherever possible and getting ready for looking at adalimumab when that loses its patent."

UK regional payer

"Well, the main drugs, the most important drugs or the most used drugs, are infliximab and adalimumab, and then when these fail we use vedolizumab now. We have to approve ustekinumab for Crohn's disease. We have also approved golimumab in ulcerative colitis, but the most used are infliximab and adalimumab."

Spanish regional payer

"They start with oral drugs like methotrexate or something of the sort, and then change over to a biologic if they fail. First of all we use infliximab, we increase infliximab's standard doses if they fail, we have a pharmacokinetic monitoring service, and when they fail infliximab we change to adalimumab, once they fail adalimumab they change to vedolizumab, and in colitis they change to ustekinumab. Golimumab is not used too much. [...] We have almost all of the drugs reimbursed in my region. In colitis we have infliximab, the biosimilar or original drug, we have adalimumab, we have golimumab, and we have one for compassionate use, maybe certolizumab. In Crohn's disease, we have all the drugs including ustekinumab [...] but we reserve it for the third line because it was approved one or two weeks ago, so at the moment we only treat patients with no other options. Beforehand, we did use ustekinumab for compassionate use in 3–4 patients, but it was not open. Now I suppose with the new approval we can expand the use for those patients who do not do well. In both cases, we have vedolizumab as well in the second line."

Spanish local payer

"There is no access control. They have full access. It must be within the label for sure. Off-label treatment is not really possible, and if the physician decides that a biologic is necessary, let us say that the first-line biologic for IBD and Crohn's is infliximab biosimilar and if this does not work for whatever reason, they can go to other drugs like vedolizumab, Stelara, or whatever."

German sickness funds payer

IBD DRUGS ARE MANAGED AS PART OF THE WIDER INFLAMMATORY CLASS OF DRUGS

Payers manage IBD drugs as part of the broader immunology and inflammation indication, doing so by product or often by class, which adds further complexity to access management. While payers have separate prior authorization requirements for use based on the indication, negotiations relating to procurement, volumes, and contracts are conducted across all indications, providing an advantage to drugs that have a wide range of approvals. For example, contract arrangements in the US for IBD drugs must take into account the impact of other more prevalent indications such as RA. This in turn has made it challenging for drugs with only one or two

approved indications to gain a foothold in the market as payers would forfeit discounts for main players such as Humira. While this practice has been largely limited to TNF-alpha inhibitors, payers expect the complexity to increase with the launches of non-TNF-alpha inhibitors, such as IL-12/23 inhibitor Stelara, which has multiple approvals in psoriasis, psoriatic arthritis, and most recently CD. Janus kinase (JAK) inhibitors also have approvals in RA, and are expected to gain approvals in UC and CD.

"As a sickness fund, we normally differentiate between those diagnoses or indications. We manage drugs as a class and so anti-TNFs as a class we manage regardless of the indications the anti-TNFs are labelled in and yes, especially the anti-TNFs are on the radar screen because it is a manageable class with the upcoming biosimilars with the treatment patterns. We do have active management, but this is not distinct to IBD or Crohn's, it is distinct to the class of drugs used."

German sickness funds payer

"We are not so much concerned about the individual indication but more about the products. The products usually have an indication not just in one of these diseases, but in [multiple] diseases. That is first of all an important consideration. Secondly, we see more and more drugs in this market, so the market gets more and more crowded. On one hand, we see new biosimilars coming, and on the other hand we see even more drugs like interleukins and JAK inhibitors, and their prices are even higher than the old TNF inhibitors. It is a big concern in Germany when we think of these indications."

German physician association payer

"We have a fairly active prior authorization program, all the autoimmune drugs are grouped together, so whether it is RA, psoriasis, psoriatic arthritis, Crohn's disease, they are all under the same giant utilization management umbrella. We look at the individual indications when we are evaluating drugs, but as far as the management policy [goes], it is quite similar, we have a tiered label, tiered specialty, and whatever appropriate first-line agents might exist are going to be the ones that are targeted."

US payer

"We do not [look at gastroenterology indications specifically], mainly because most of the drugs in the class have a breadth of indications; in fact, that has been an issue with some of the drugs with narrow indications like psoriasis."

US payer

"In each disease, we have an amount that the CatSalut, who is the payer, pays us. For instance, for arthritis they pay I think around 800 euros per patient per month, and in the case of gastroenterology diseases they pay 1,108 euros per patient per month. It is different, and psoriasis also has a different reimbursement index."

Spanish regional payer

Table 3: **Levers impacting access to IBD drugs in the US and five major EU markets, by country**

	US	France	Germany	Italy	Spain	UK
National	n/a	TC assesses benefit of new drugs over comparators. Reimbursement confined to patient population indicated in evaluation. TC has completed assessments for Entyvio, Humira, Remicade, Simponi (UC), and Stelara (CD). Stelara and Entyvio (UC) received minor added benefit	G-BA assesses new products for added benefit over comparators, impacting price negotiations. Entyvio received no added benefit. Stelara is expected to be excluded from AMNOG assessment	AIFA decides on reimbursement and pricing of all new therapies. All biologic medications approved in class H are reimbursable in hospital settings with a limitation to specialist prescribing only. Remicade and Inflectra are subject to AIFA monitoring for pediatric UC. Humira and Simponi are subject to AIFA monitoring registries for adult UC. Entyvio is reimbursed in the third line for CD	AEMPS conducted IPT assessments for Entyvio in CD and UC. Reimbursement is restricted to TNF-alpha inhibitor-refractory patients	NICE assessed Entyvio, Humira, Remicade, Simponi (UC), and Stelara (CD). Entyvio restricted to third line in CD, with a PAS for both UC and CD. Simponi requires a PAS. Remicade restricted for severe CD, but is reimbursed for moderate and severe UC and pediatric UC. Stelara is reimbursed according to its EMA label. Price is based on discount agreed with the CMU

Table 3: **Levers impacting access to IBD drugs in the US and five major EU markets, by country**

Regional	All biologic DMARDs subject to PA. Payers use formulary tiering or step therapy to promote preferred brands and contract for drugs as part of inflammatory segment, which provides an advantage for drugs with the largest number of covered indications	Formularies not used	Some regions subject TNF-alpha inhibitors to prescribing limits (Richtgroessen), while in others they are exempt. Regions are in flux, with some moving away from prescribing limits, with biosimilar quotas being the most common cost-containment mechanism. In the future, some regional sickness funds may contract for preferred agents through tenders	Regional formularies dictate availability of RA drugs. Regions set budget limits for drug expenditure in hospitals. Emilia-Romagna considers TNF-alpha inhibitors as first-line biologic options. Entyvio is reimbursed in the third line for UC	Regional and GENESIS reports utilized to assess added value and/or benefits. Regional committees set guidelines for restricted drugs, but these are not prescriptive. If regional guidance is absent, hospitals set availability of drugs and/or negotiate with drug manufacturers directly for local discounts	Regional decision-makers must follow NICE TAs. Regional payers use formularies to determine brand preference, although these are not binding. Biologics are purchased through regional procurement contracts, providing an opportunity to compete on price for preferred position

Table 3: **Levers impacting access to IBD drugs in the US and five major EU markets, by country**

Physician incentives and controls	Physicians must try preferred brands, most often Humira, prior to accessing non-preferred brands	Follow national guidelines and reimbursement set by TC. Initial prescription limited to hospital setting. Inclusion on "liste en sus" critical for access to IV drugs	In some regions physicians are incentivized to fulfill quotas set by sickness funds for preferred drugs, which can influence prescribing of the cheapest agent through regresses and audits. Physicians in some regions are asked to mainly prescribe TNF-alpha inhibitors for which discount agreements are in place	Specialist centers and hospitals must stick to budgets on drugs set by regions. Restricted to hospital use only. Physicians follow therapeutic plans set by regions	Restricted to hospital use only. Physicians/hospitals follow regional guidelines set forth and receive payment for utilization of drug by indication	Physicians follow guidelines set by NICE. Physicians must fill group patient approval forms for biologics
Patient incentives	Patient co-pays in place, insurers use co-pay differentials to drive patients toward preferred brands	n/a	n/a	n/a	n/a	n/a

AEMPS = Spanish Agency of Medicines and Medical Devices; AIFA = Italian Medicines Agency; AMNOG = Act on the Reform of the Market for Medicinal Products; CD = Crohn's disease; CMU = Commercial Medicines Unit; DMARD = disease-modifying antirheumatic drug; EMA = European Medicines Agency; IPT = therapeutic positioning report; IV = intravenous; NICE = National Institute for Health and Care Excellence; PA = prior authorization; PAS = patient access scheme; RA = rheumatoid arthritis; TC = Transparency Committee; TNF = tumor necrosis factor; UC = ulcerative colitis

Source: Datamonitor Healthcare's proprietary primary research interviews with key opinion leaders and payers, August 2017

THE LARGEST UNMET NEED IN UC AND CD IS SEVERE PATIENTS AT LATER LINES OF THERAPY, WHERE OPTIONS ARE LIMITED

Despite the launches of non-TNF-alpha inhibitors Stelara and Entyvio, patients with severe UC and CD and those who are refractory to available therapies continue to present a high level of unmet need from both payers' and physicians' perspectives. Stelara and Entyvio do not have significantly superior efficacy and safety compared to TNF-alpha inhibitors according to physician experience, and the drugs have only received ratings of either minor added benefit or no added benefit in French and German health technology assessments (HTAs). Additionally, some physicians report that patients lose efficacy with their current treatments, and cycling often needs to occur, but with only three novel mechanisms of action the options are narrowed quite quickly. Datamonitor Healthcare therefore anticipates that payers will be receptive to pipeline drugs specifically aimed towards patients at later lines of therapy as such drugs have the potential to delay the last-line option of surgery for many severe patients.

"That is always the last-line patients who have failed on every other drug and that, I would say, is a very severe patient. So, severity of the disease is crucial, and line of therapy is crucial."

German physician association payer

"Severe patients are not controlled with first-line drugs. Vedolizumab is expensive, and ustekinumab is more expensive than the first-line treatment. Second-line treatments from a payer perspective are a budget problem, ie vedolizumab and ustekinumab."

Spanish local payer

"I think some of those difficult patients at the end of the line that do not have many treatment options. We get quite a few individual funding requests for these patients to apply for new therapies, and the reason is because they are not suitable for surgery or wanting a delay to surgery. When I speak to my clinicians I think biologics work very well for these patients. It is when they no longer respond to biologics that they have limited treatment options."

UK regional payer

"The unmet need is very high, for two thirds of the population, but for one third of the population, those who are good responders to anti-TNF-alpha, [...] for those patients the unmet need is zero. So, if you want to beat the anti-TNF-alpha you have to demonstrate [superiority] – because then the agreement would be that we would never reimburse in first line. It is not a matter of price even if you are slightly cheaper if you are not as good [it will not be reimbursed], especially because we know that infliximab biosimilar is likely to become cheaper and cheaper, it would be most likely even in some way included in the [Diagnosis-Related Groups] in the long run, so in a way we will not pay for it. [...] In other words, the unmet need is still perceived as quite high because those biologics give a partial response, but we are far from stopping the progression of the disease, or even a cure, or even bringing a patient up to remission for a substantial period of time is pretty low, and it is probably even worse in the real world. [...] Now, for the HTA, I would say a concern is more about the effectiveness, because obviously ASMR IV and sometimes even worse ASMR V and a low SMR, such as moderate for Crohn's disease for vedolizumab in the second line, or insufficient in the first line for vedolizumab, is a good signal about the lack of very clear effectiveness in those two indications by the HTA body."

Former French national payer

"Well, one of the problems is that not all the patients respond to treatment. Only 30% or 40% of patients respond, and also the treatments, in the majority, are administered in hospital by IV infusions. That is a problem. Also, we have not so many different drugs that act to different sites and offer not so many possibilities to the biological treatments now. The agents that we have are well tolerated, but the possibilities to have infections, serious infections, and other side effects are important also. I think that the most important is that the treatments, over time, lose efficacy for different reasons. We need new drugs and new agents that act in different sites."

Spanish regional payer

"Severe patients are quite young people, so in order to avoid surgery I suppose we will use the new drugs, effective drugs, and they will switch to those kinds of treatments. We currently have patients with no options, we do not have any treatment options for these kinds of patients, and we must offer a solution for those patients at least for a few years before surgery. Surgery is not always a resection, sometimes it is surgery with a hole in the abdomen, an anastomosis, and so these are very complicated patients."

Spanish local payer

ACCESS TO RECENTLY LAUNCHED AND PIPELINE PRODUCTS

INSIGHTS AND STRATEGIC RECOMMENDATIONS

Stelara (Crohn's disease)

- Despite wider reimbursed populations in some countries, Stelara (ustekinumab; Johnson & Johnson/Mitsubishi Tanabe) is most likely to be used among patients after TNF-alpha inhibitor failure than it is among earlier lines, as payers are eager to take advantage of cost savings from biosimilar TNF-alpha inhibitor launches. In some countries, such as France and Spain, Stelara's use is limited to TNF-alpha inhibitor-failure patients due to the availability of only placebo-controlled trial data.

- Stelara's faster onset of action detectable during the intravenous (IV) loading dose could put it ahead of Entyvio (vedolizumab; Takeda) according to some payers. Others, however, are more skeptical regarding this anecdotal evidence, and believe that although Stelara has a faster onset of action, it has demonstrated issues with regard to partial responsiveness.

- Stelara could further position itself favorably by offering a free IV loading dose, a strategy that is being used in the UK market. The advantage of such an approach is that responders are identified quickly during this induction phase, allowing positioning ahead of Entyvio. Other payers say that while triaging patients is effective, there is an additional cost and administrative burden associated with IV drugs.

Etrolizumab (ulcerative colitis)

- Etrolizumab's (Roche) head-to-head trial against infliximab in TNF inhibitor-naïve patients for the ulcerative colitis (UC) indication is the first active comparator trial in inflammatory bowel disease (IBD), but payers say that reimbursement in this population is not likely even if superiority is demonstrated unless substantial pricing concessions are made. The launch of biosimilars and payers' existing contracts with branded TNF products, as well as physician familiarity with the TNF-alpha inhibitors, will make it challenging for etrolizumab to gain a foothold in this market.

- Payers would prefer head-to-head trials against non-TNF-alpha inhibitors such as Entyvio or Stelara in TNF inhibitor-failure patients instead of a trial against placebo, as the latter does not allow for an added benefit rating. Etrolizumab's trial includes an active comparator arm against adalimumab, but this is used a secondary endpoint, which may not be able to claim statistically significant superiority.

- Etrolizumab's placement in the therapeutic pathway will hinge on its pricing compared to biosimilar TNF-alpha inhibitors. A price equivalent to biosimilar TNF-alpha inhibitors indicates possible positioning in the first line, while a higher price would relegate the therapy to later lines.

- Etrolizumab's subcutaneous (SC) formulation will not confer it an advantage over Entyvio, as the latter's SC formulation is expected to be approved before etrolizumab. Therefore, etrolizumab will need to demonstrate significantly better efficacy in order to be differentiated within the alpha integrin class.

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Oral compounds

- Without head-to-head trials, oral compounds entering the IBD market will face difficulties in achieving differentiation based on clinical efficacy and safety, leading toward pricing being the differentiating factor among the products. Indirect comparisons are not likely to benefit the drugs as most trials have differing clinical trial designs, making such analyses challenging.

- Payers have reservations regarding oral therapies serving as the step before patients move on to biologics, and they are more interested in upcoming therapies that are more effective than the standard of care. Others see some limited use for oral compounds such as in those with moderate disease, or in patients who present with complications, which may allow the oral compounds to carve a niche within the IBD market.

- US payers are especially challenged in positioning oral therapies as a bridge to TNF inhibitor therapy as existing contracts with branded TNF inhibitors may be disrupted. Further, as Humira (adalimumab; AbbVie/Eisai) and Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) have approvals in multiple indications, upsetting the contract could mean a big loss for payers. Humira and Remicade need to move towards indication-based contracting before payers would take the chance of contracting for oral-based therapies.

- Payers are likely to leverage contracting when all four oral compounds have launched in the market. Some payers plan to put all of the products in one oral category, while others are likely to include all products as long as the price differences are minimal. In this scenario, physicians could prescribe ozanimod (Celgene) as a bridging therapy, while Janus kinase (JAK) inhibitors, with greater efficacy, could be used in both TNF-naïve patients and as an option after TNF failure.

XELJANZ (ULCERATIVE COLITIS)

- Of the key oral agents in IBD, payers are looking forward to Xeljanz's (tofacitinib; Pfizer) launch due to both its oral formulation and the strong efficacy data demonstrating sustained remission. Despite this, payers are still conflicted regarding the consequent positioning, with some advocating for Xeljanz as an early bridging therapy, while others want to place the drug after TNF-alpha inhibitor failure. Pricing is likely to determine Xeljanz's placement in the therapeutic pathway, with a price in line with TNF-alpha biosimilars potentially meaning access to early lines of therapy. In Europe, pricing for Xeljanz in IBD will be key, as there is no indication-specific pricing. The drug's pricing will hinge on its launch price for rheumatoid arthritis (RA) as this is the drug's first approval. Further, Pfizer will need to also contend with the pricing strategy of Olumiant (baricitinib; Eli Lilly/Incyte) in RA, as it came to market for RA ahead of Xeljanz in the EU.

FILGOTINIB (ULCERATIVE COLITIS AND CROHN'S DISEASE)

- Filgotinib will need to differentiate itself from Xeljanz via further pricing concessions, despite the drug's advantages over Xeljanz, including use in both UC and Crohn's disease (CD), as well as Phase III data for CD patients who are refractory to TNF-alpha inhibitors and to Entyvio.

OZANIMOD (ULCERATIVE COLITIS AND CROHN'S DISEASE)

- Ozanimod's perceived increased safety is not likely to be an advantage in the minds of payers as efficacy remains their top priority. Payers expect the drug will be positioned as a bridging therapy, and will therefore need to lower its price (below that of biosimilar adalimumab or infliximab) to attain access earlier in the treatment pathway.

- Ozanimod's approval in UC could have negative pricing implications in multiple sclerosis (MS), as the price benchmark in MS is much higher than in UC. In some markets, this could mean ozanimod will need to be priced in line with its cheapest indication, or else risk not being reimbursed in UC. Despite this, there are examples where manufacturers have launched with two brands for two indications to allow for different pricing. Celgene may need to consult the launches of similar products, such as everolimus, to ascertain its optimum strategy.

PAYERS ARE UNIMPRESSED BY STELARA'S PLACEBO-CONTROLLED TRIALS

Payers are critical of Stelara's placebo-controlled trials, especially in anti-TNF-naïve patients. Additionally, indirect comparisons have proven impossible to carry out as Stelara's trials had differing patient populations and time points. Payers also take issue that Stelara's own results against placebo were lackluster, and that the drug did not demonstrate an impressive difference. Payers express a bit more enthusiasm for Stelara as an alternative therapy after TNF-alpha inhibitor failure, as patients in this stage have few other options. Therefore, in many markets, access is restricted to second-line biologic use. Datamonitor Healthcare anticipates that payers will continue to relegate Stelara to later lines of therapy to allow less expensive options, especially biosimilars, to be explored first.

"The only question is are you as good, [...] especially when the standard of care is very well established, and that is clearly the case for anti-TNF-alpha. If you have a placebo in the anti-TNF-naïve population, then the question is can you draw an indirect comparison, and sometimes you have some caveat because the inclusion criteria are not exactly the same, the endpoint analysis might be at different times, and so on and so forth, so usually it is small studies with 300 patients, 400 patients, so it is very difficult. In other words, the margin of non-inferiority is huge, and therefore it might be they do not say you are non-inferior, they just say you have not demonstrated non-inferiority, therefore you cannot claim it.

The classifications were almost not there, the length of the studies was different, the endpoints were somewhat different, so it was almost impossible to do an indirect comparison, and most of the indirect comparisons were rejected. They might be sufficient for a cost-effectiveness analysis, they are clearly not sufficient for purely traditional clinical effectiveness. So, it is very standard that the French, when you have a very well established standard of care, would reject reimbursement in the first line when you do not match non-inferiority. I would say the disappointment was not just the design, but also the effectiveness against placebo is very small."

Former French national payer

"The question is, is it efficient, and given the fact that Stelara is much more expensive than an infliximab biosimilar but cannot be restricted by patient population [etc], we would have a stronger view whether the first-line options were exhausted prior to the Stelara usage. If there is clear medical indication, the patient can claim for it and get this drug."

German sickness funds payer

"The point of this drug is that it has been studied versus placebo, and of course this reprises the point of why it was studied versus placebo, and how we can eventually fix the place of this drug in therapy when in fact it is compared to placebo. The answer that is from the company holding the drug is that since there is no alternative, the use of placebo in this case is justified. In a way that is a good answer because this is a clinical unmet need, and when in a field there is no alternative of course the clinical trial can be built with a comparison versus placebo. [...] What AIFA will say for sure is that OK, we can approve this drug for patients with this disease, but since the patient population is composed of TNF-refractory patients and TNF-naïve patients, and this is the level of the drug, we will approve and reimburse the drug only for TNF-refractory patients and not for TNF-naïve patients because of course, TNF-naïve patients can be treated effectively with TNF inhibitors."

Former Italian national payer

"I think what we are going to find is it is going to become a bit like RA. A whole mixing pot of various different biologics that are all able to be used for the same condition where we are not necessarily doing sequential therapy. At the moment NICE does not say just keep treating repeated failures with one biologic and switching to another, so I think what is going to happen and what we saw in RA anyway was you have the immunosuppressants first, anti-TNF becomes standard of care using biosimilars; however, they will allow, probably, maybe two or three cycles of patients to go through a fixed number of sequential therapies. Let us say we allow three, so you allow three, but they might suggest a different mode of action biologic. So, they might say: 'look, once you have had anti-TNF, there is no point giving another anti-TNF, maybe we go for interleukin.'"

UK local payer

"I can tell you the fact that I do not know about it six months later means it is a non-event and it has not changed anything for us. Stelara is not a preferred drug on our formulary, so whether it be for psoriasis or psoriatic arthritis you have to have tried and failed either Enbrel, or adalimumab, or infliximab [...] because really it is missing 50% of our patients in rheumatoid and other inflammatory diseases. I think we can still step it through the TNFs because again it is not going to show superiority. It is a placebo-controlled trial, it looks like there are TNF-alpha-failure patients in there, but I do not think it is going to be enough to say that it is a comparative."

US payer

"So, I think ustekinumab is being seen as an attractive option. As I say, my consultant has already asked if he can use it [...] very keen to use it in a number of patients and particularly for those that have not responded to existing anti-TNFs. I am hoping [the use will] not [be in first line] because it is more expensive. The IV induction, that is low cost. The rest of ustekinumab is the same price as in its existing indication."

UK regional payer

"This [addresses] a clinical unmet need that we have in [...] Crohn's disease, because of course in the algorithm for the treatment of this disease there is actually no space for other drugs in the case of failure of TNF inhibitors in these patients."

Former Italian national payer

"You just have to try and fail Humira before you can get it, like everything else."

US payer

Some payers argue that Stelara's faster onset of action is an advantage over Entyvio, while others are skeptical

Stelara's faster onset of action, which is usually detectable during the IV loading dose, could put it ahead of Entyvio. Both Stelara and Entyvio are not likely to be used ahead of TNF-alpha inhibitors, as physicians have more familiarity using Remicade and Humira, and payers are seeking to take advantage of the lower cost of biosimilars. Some physicians, however, may choose to use Stelara over Entyvio to assess response as their clinical experience has shown that Stelara has a faster response compared to Entyvio, making it easier to ascertain from the initial loading dose if Stelara is going to be effective and whether to keep patients on the drug. Others, however, are more skeptical, in that there are no head-to-head trials and no clinical trial data that captured the information, and the anecdotal evidence is not credible enough to result in favorable positioning. Further, some payers highlight that the advantages of starting with Stelara over Entyvio may lead to issues with partial responders, something that is not commonly encountered with Entyvio. Datamonitor Healthcare anticipates that payers will be likely to choose Stelara over Entyvio if it can demonstrate that the maintenance costs associated with opting for Stelara will remain competitive after the initial loading dose discount.

"Well, I am not sure whether [judging between faster and slower responders is] just physicians anecdotally, or if that is something that is in the data sense, comparatively."

UK local payer

"[The faster onset] might be just a treating physician's perception, and secondly for payers that is not crucial."

German physician association payer

"[Stelara's faster onset] could be [used earlier], but not in first line, always in second line. Stelara is currently one of the most expensive drugs."

Spanish local payer

"[Stelara] is currently in third line. In future, it will probably be in second line instead of vedolizumab, and vedolizumab would be in third line. In my opinion, vedolizumab in Crohn's disease – well, and in colitis – is a little bit slow. You start treating with vedolizumab and the patient responds in a month – it is not an immediate response, it is in a month, and it is a drug that is a little bit difficult to manage because sometimes the patients do not have immediate success. Then, Stelara does not have this mechanism of action, and the patient responds quite quickly. For example, we had a patient at the hospital last week that responded in two days. We administered Stelara and in two days it showed improvement of parameters."

Spanish local payer

"I think vedolizumab takes longer than ustekinumab, and ustekinumab has got an IV loading dose. What the companies are marketing is that you can pretty much identify from the IV and this induction dose whether you are going to get responders, whereas vedolizumab takes longer, but I think what my clinician has discussed with me is that patients either respond very well or not at all. There is no kind of that midline in terms of a responder for vedolizumab, so it is quite easy to go: 'yes, leave them on,' or 'no, they are not getting any benefit.' It is when you get that partial response that it is sometimes difficult, whereas we do not see that with vedolizumab, but you are correct it takes longer to see a response, and of course ustekinumab, after the IV which I think they have priced at a pound or something ridiculous, so it costs us nothing to see whether there is a responder or not. Then it is only the subcutaneous ones that we would continue to pay for when the charges become significant."

UK regional payer

"Well, I think that vedolizumab has a different mechanism of action with a different target, and I think that is the most important thing of vedolizumab. The target of Stelara also is a different target. [...] With vedolizumab the drug effect appears later – I think that is a characteristic of the drug, but it is not very important because if you know that that happens the physicians have to evaluate the efficacy of this drug at the right time. I think that is my opinion. It will maybe not definitely affect the choice of the drugs.

I think that in general the position would be firstly the same as now: infliximab, adalimumab as the first step, and if that fails we can begin to ustekinumab, and if ustekinumab fails I think vedolizumab maintains the first [choice] in the fourth line of treatment. I think that may be the future. I do not know, but I hope for that."

Spanish regional payer

Offering a free IV loading dose for Stelara may give it a further competitive edge in some markets

In the UK, Stelara's first IV loading dose is offered free of charge. The rationale behind this approach is that given the drug's fast onset

of action, responders can be identified quickly, and the manufacturer aims to utilize this strategy to ensure the drug is positioned ahead of Entyvio. While this may be seen as attractive by some payers, others have highlighted the additional cost and burden associated with IV administered drugs. Datamonitor Healthcare anticipates that where allowed, providing subsidized initial dosing can help payers save money, but manufacturers need to ensure that doing so does not create further burden elsewhere for the payer. Otherwise, a simple discount scheme may be a more optimal solution.

"Well, the issue [with giving a loading dose for free] you have got here is that free, cheap initial dose has got a health utility cost because it has to be given intravenously, and that is actually a bigger negative than even the cost of the drug [because of the associated cost of administering it]."

UK local payer

"The offers change and all the companies make similar offers. Adalimumab makes a lot of offers now because adalimumab biosimilar becomes available in 2018, and then all the others – Remicade, for instance – decrease the price because we have biosimilars and we use biosimilars in naïve people. I think that the offers or the discounts from the companies are given very often."

Spanish regional payer

SUPERIORITY DATA AGAINST INFLIXIMAB ARE UNLIKELY TO PUSH ETROLIZUMAB TO BE A FIRST-LINE BIOLOGIC

Payers welcome etrolizumab's head-to-head trial against infliximab, as the drug is the first to have an active comparator trial for the UC indication, but they do not expect reimbursement for first-line biologic use. Even if etrolizumab proves superiority to infliximab, respondents say that it will be particularly challenging for the drug to be placed among first-line TNF-alpha inhibitors given the availability of biosimilar infliximab and expected biosimilar adalimumab entry. US payers also report that putting etrolizumab at the first line among TNF-alpha inhibitors would jeopardize their long-standing contract for Humira as a preferred product. Payers do not expect a great degree of opposition from physicians, whose conservative prescribing practices will likely result in a preference for TNF-alpha inhibitors initially. There is an additional fear that if patients use etrolizumab prior to TNF-alpha inhibitors, they would not be able to step back into TNF-alpha inhibitors should etrolizumab treatment fail. Datamonitor Healthcare anticipates that first-line use of etrolizumab will be highly restricted to patients who are intolerant of or contraindicated to TNF-alpha inhibitors, or who have highly severe symptoms.

Any claim on etrolizumab's superiority versus infliximab is likely to be scrutinized in great detail before a decision on a level of added benefit is made. Additionally, payers are hoping for at least a 5% improvement against infliximab, although many are predicting that a greater improvement needs to be achieved for the drug to gain significant additional benefit ratings.

"So, the question is, is the study powered to demonstrate maintenance of remission against infliximab at 52 weeks. [...] So, maybe they are in a position to demonstrate non-inferiority against infliximab. What is very important is to know whether the [GARDENIA] study was designed to demonstrate superiority or just non-inferiority, and if yes, how they have defined the margins for non-inferiority. That would be the question asked by the Transparency Committee to the sponsor."

Former French national payer

"I think there is room for additional therapeutic options, and it is OK to divide into TNF-alpha-naïve and TNF-alpha-failure patients, but regarding the naïve patients, I think 5% difference in superior efficacy at week 54 is OK. It could be enough for an additional benefit against infliximab. It is a bit on the sharp edge whether the drug can get an added benefit or not, because only this one subgroup [has] superior efficacy versus infliximab."

German physician association payer

"Here we have again the two kinds of populations, the TNF-naïve and TNF-refractory. For AIFA, the second group is much, much more important [...] We have so many drugs for TNF-naïve patients that there is no sense of studying new drugs for TNF-naïve patients. There is always a possible case of a patient that is intolerant to infliximab, and of course in that case you have to treat that patient with another drug, but these are particular situations. The point here is not related to the double indication."

Former Italian national payer

"If you have a 10% absolute improvement in achieving remission at week 6 or week 8, and this 10% remains the same at week 52, and it is powered for both – so induction and remission – usually it is two different studies, so it is demonstrated as a primary endpoint but it can be a co-primary endpoint, it is not an issue at all, and if it is well designed and well powered and you have 10% absolute difference, then for sure you would get ASMR IV. If you have let us say 20–30% difference you would get ASMR III, if you have 50% difference you would get ASMR II, and so on and so forth, why not? Because if you look at the baseline it is pretty low for these patients. [...] If I have 60–80% of the patients in remission at 52 weeks instead of, maybe, I do not know, 10–20% today, it would be a huge difference, and you would gain an ASMR II. Now, if the absolute difference is just 10%, it is better than nothing, you would get an ASMR IV."

Former French national payer

"I think that maybe 15% or 20% [better than infliximab in terms of performance] for instance. I do not know."

Spanish regional payer

"[A relative improvement of 5% is] too small. That is no additional benefit rating. 15% [is the minimum we would need to see for an additional benefit rating]."

German physician association payer

"The head-to-head trial is of interest, but it is interesting how cost effective it will be when you do the pricing against it. So let us say it is 5% superiority, that does not leave a lot of space for pricing above a biosimilar price. It almost becomes academic because that almost might allow you a 5% price over biosimilar, which would not be commercially viable. So even if it is 5% better head to head, [...] I think the ICER will still be high on the NHS, but even though the ICER is high I think that the pricing will be in line with expected branded treatments. I think, in a way, [...] what becomes a more valuable feature in the access are the different modes of action. So, what we see in the beginning is mode of action is less important than efficacy, but once we have now got a commodity pool of biosimilars that we can use for first-, second-, third-, fourth-, fifth-, sixth-, seventh-line treatment, they are all anti-TNFs. This is where sometimes having something which is maybe a different mode of action, like an interleukin pathway drug or this one is like an alpha 4 beta – I have never heard of that – it may actually be of more value, but I have to see more value in the pathways from different modes of action. Like if this was just another anti-TNF there would be trouble, big trouble.

I do not see how any new treatment coming in now would displace a TNF that is a biosimilar price regardless of its evidence, unless it is like a cure or something. I do not think a new branded biologic will be able to be competitive to a biosimilar price, so I do not think the strategy can be to do that. What they have to do is compete against the other brands playing in the post-biosimilar space."

UK local payer

"Well, then I think if it is not superior, then it is basically just any product in the mix. You have to still try and see the first-line options, the prior authorization of the label – must be prescribed by a specialist, step through Humira first – so all the standard criteria we have in place today for other competing therapies. [If it demonstrates superiority to infliximab] our answers are probably the same. It is OK for us to require adalimumab first because a lot of people do respond, and if they did not respond then they could move on to this drug, but we want to

protect our adalimumab contract.

I do not think [first line] is likely to happen. Again, we have too much money and resources and utilization tied up in Humira as our preferred [option]. So, if you look at other agents that have launched since then including Entyvio, which you could argue is a better agent than adalimumab, we still step through adalimumab before we give Entyvio. [...] I mean, if they priced it the same as the biosimilar that would make no sense. But if they did that, then certainly that would be a possibility, but I think we would be fearful that they would raise the price if they were not successful in getting utilization."

US payer

"Especially for severe patients; when patients are controlled, they are controlled for a time period, I do not know, one or two years or maybe less, so if we use this drug I do not know if it is possible to switch to infliximab again. If we had a study saying that you can recover the use of infliximab, it would be interesting to use one before the other. The patient can change from one to another depending on price – the same model that we have with infliximab and adalimumab."

Spanish local payer

"I think [physicians] are mainly [OK with stepping through TNF-alpha inhibitors] because they have been very comfortable with the TNFs, and doctors are creatures of habit, they use the drugs they know; that does not mean they will not use new drugs, there are some early adopters, but they have not been particularly noisy about wanting the IL-12/23, and IL-17s, and anti-IL-6 or whatever else is out there. I think that will grow as they get more comfortable using the newer agents in a group of patients. There is probably a day of reckoning, I just do not know when it is going to be."

US payer

"At the beginning of the commercialization it would probably be after infliximab, we must consider price – our problem is there, one positive point is the subcutaneous administration and superiority to infliximab, but because of experience, price, we would reserve this drug for those patients who failed infliximab, so probably in second line, that is my opinion at least. [Even at a comparable price to biosimilar infliximab and with demonstrated superiority to infliximab] there would probably be fewer restrictions, but in my opinion it would still be in second line."

Spanish local payer

Payers would have preferred an active comparator trial in second-line patients

As part of its evidence package, etrolizumab is also being tested in TNF-alpha inhibitor-failure patients, but payers state that the design against placebo as the primary comparator hinders their ability to assess the drug and give an added benefit rating. While there is an active comparator arm against adalimumab, payers also take issue with this as it is used to test a secondary endpoint instead of a primary endpoint, which means it may not be properly powered for statistical significance. Datamonitor Healthcare anticipates that since etrolizumab is not likely to receive an added benefit for treatment failure patients from health technology assessment (HTA) bodies, the drug will be priced comparably to Stelara and Entyvio.

"Placebo superiority means nothing; placebo is not an option for these patients [...] they will get Stelara or they get whatever but not placebo. [...] Better efficacy over adalimumab is only at week 10, which is a problem because the German framework requires, in chronic diseases, at least a 26-week study duration. [...] And so there is also no additional benefit in the anti-TNF-failure patients with this placebo control."

German physician association payer

"The first primary [endpoint] is induction of remission compared with placebo, so it is interesting but quite irrelevant. [...] What is the indirect

comparison from HICKORY and LAUREL with vedolizumab, because it is the same mechanism of action. Is it non-inferior? [...] So the best you may achieve for this drug would be ASMR V in the second line."

Former French national payer

Positioning will ultimately depend on pricing compared to biosimilar TNF-alpha inhibitors

Etrolizumab's market reach will ultimately be determined by Roche's pricing strategy for the product. In countries where pricing is determined through negotiations, the target patient population in which manufacturers seek reimbursement will be the key determinant of the negotiated price. Similarly, in markets with free pricing such as the US and UK, the drug's launch price will drive payer decisions regarding reimbursement for different patient subgroups. In the UK, if etrolizumab is priced on a par with biosimilar TNF-alpha inhibitors, some payers have stated that there is a possibility to use the drug alongside TNF-alpha inhibitors or even ahead of the group, as etrolizumab will have head-to-head data against adalimumab and infliximab. On the other hand, a higher price is likely to result in the drug's use after TNF-alpha inhibitors.

To achieve access as a first-line biologic, most payers agree that pricing similar to biosimilar TNF-alpha inhibitors will be required. This pricing benchmark, however, will continue to be a downward moving target as more biosimilar TNF-alpha inhibitors are launched. Roche could utilize a similar strategy as was used to launch baricitinib in the UK at a major discount well below the price of TNF-alpha inhibitor biosimilars, allowing etrolizumab to be placed ahead of the biosimilars. Roche will need to evaluate if this strategy will be worth sacrificing the higher price for first-line access, or if it would like to position the drug competitively with other second-line medicines such as Entyvio and Stelara, where it could maintain a higher price.

"Because of the biosimilars coming into the mix and the prices that are likely, I would imagine this will be after biosimilar, unless – and I might be pleasantly surprised because I have been with Lilly with baricitinib – they may decide to price it competitively with biosimilar, in which case because they have got the superior efficacy data against adalimumab then if it was the same price I would use it before TNF. But, for a premium, I am going to try the biosimilar first because it will maybe work for some patients and it will cost me less. So, it will depend on price. [...] Because it is subcutaneous again, I might struggle to use it instead of infliximab because there is cost obviously associated with IV, so my more likely comparator was adalimumab because of the route of administration.

[If it is more expensive than TNF-alpha biosimilars] then it is about uptake, so we would have to put it in our pathway, but it means we may put it in our pathway as an option after some of the other existing cheaper options. [...] So clinicians will have access to it, but they may not be using a huge amount. We have ways of encouraging them to use the most cost-effective [therapy], and agree and monitor and audit them and make sure that because when you have got a number of NICE options you can still have a preferred first-line option."

UK regional payer

"What is the price assumption, are they happy with a biosimilar-like price and to have the full market, and have a very good market penetration in a short period of time, which might be a strategy for them especially because the list price of infliximab biosimilar is quite high in France again, because of this mechanism. Then you could have what we call a fast track, you can claim reimbursement saying I am as good as vedolizumab in second line, and infliximab in first line, therefore you anchor your price negotiation, so you can be at the price of the biosimilar, so the weighted average price of the two target populations between vedolizumab and infliximab biosimilar with of course a discount in order to gain quick market access. For example, you are almost at parity with the biosimilar price, but you can also treat patients in second line, again a huge market penetration. It is not that your price negotiations are likely to be very long because the economic committee would have an advantage to have many competitors and say in any case we can wait, how many integrin drugs are in the pipeline in second line, how many other drugs with a different mechanism of action such as anti-IL [...] and so on are in the pipeline coming for those indications that can compete on price. If you have huge pressure the economic committee would try and take an advantage."

Former French national payer

"It depends a bit on the adequate comparator for the failure patients. If vedolizumab and Stelara are the adequate comparators and you have no added benefit, then you can still [have] their price for this subgroup. I think it is a huge negotiation in this case because the Federal Association for Sick Funds will rely on the latest infliximab biosimilar price I think, for the [TNF-naïve] subgroup. For the failure patients, it is easier [...] and the result will be a weighted average between the current Stelara price and the biosimilar price, but I think it is a crystal ball to be more precise where this weighted average will be in the end."

German physician association payer

"Well, it depends on price, with less efficacy or equivalent efficacy compared to current treatment, I would prefer to use infliximab. If the price is too expensive we would use adalimumab, and then this product could be in third line. [At the moment] just infliximab is sufficient."

Spanish local payer

Payers look forward to etrolizumab's SC administration, but Entyvio also has an SC formulation in development

Payers are excited about the development of SC-based etrolizumab and Entyvio due to their ability to reduce healthcare resource use and costs associated with IV administration. Payers cite that IV administered drugs are associated with additional burden such as nursing time, facility costs for infusions, and pressure on bed occupancy. Additionally, an SC formulation will also provide an alternate option for patients who cannot easily visit infusion centers, or who prefer more autonomy in administering their drugs. IV options remain useful, however, for patients who do not want to administer their own medicines, and Entyvio will still have a market share among this niche group. For now, patients, physicians, and payers are limited to Entyvio IV as the only non-TNF-alpha inhibitor biologic option in UC, and will need to account for additional administrative costs and resource constraints.

Etrolizumab's SC administration could provide an advantage over Entyvio, but only if the drug were to launch earlier than Entyvio's SC formulation. However, currently Entyvio SC is expected to launch in 2020, while etrolizumab is set to reach the market in 2021. Datamonitor Healthcare expects that given similar pricing and efficacy, the choice between Entyvio SC and etrolizumab SC would be left to physicians.

"Well, etrolizumab has the same mechanism of action, but with some differences compared to the vedolizumab. But in the aspect of the administration route, I think that there may be differences between patients. A group of patients prefer the administration by day hospital, by IV, for instance patients that are not working or are retired or they are scared of the auto-injection. [...] Patients that are working prefer the subcutaneous administration."

Spanish regional payer

"I think it is more or less up to the physician to decide between Entyvio and [etrolizumab], but again I think he will regularly decide for the subcutaneous option, if he can, but it is unlikely that the sick fund encourages one or the other."

German sickness funds payer

"That is true, the day hospital is full and we do not have places in the day hospital. We prefer the auto-administration, the self-injection for the patients. We prefer that because these drugs are presented in different forms of syringes or mechanisms and devices that are easy to use, and we prefer that."

Spanish regional payer

"Yes [if the price were the same, SC would be preferred, but if the price were higher than Entyvio], then I would prefer vedolizumab. We would maintain infliximab, this could be our option when they failed other drugs – well it would be another option to treat patients when they failed infliximab, but we would always start with infliximab."

Spanish local payer

"I think [SC administration] makes it more appealing from the patients' and physicians' perspectives, because a lot of these physicians have infusion places but they are not really reimbursed for infusions. They get a quarterly lump sum, and if they have to provide infusions for the same quarterly lump sum, they lose money, so to say, but for the sick fund it does not matter because we do not pay for these infusions. We pay the quarterly honorarium or lump sum for the physicians and so, if it is not hugely more expensive but it is subcutaneous, I think it is a reason for the physician to prefer the subcutaneous treatment because it brings down [their own costs]."

German sickness funds payer

"[Etrolizumab] has come up on our horizon scanning as a new molecule. I think, certainly the data I saw, it has met its primary endpoints in the trials to date. It is subcutaneous, it is every four weeks, so yes, it will be another option I guess for those patients at biologic level."

UK regional payer

"[Etrolizumab] is subcutaneous, it would be the pharmacy benefit, it has some superiority data, and if it is priced right it could theoretically become the preferred agent. It has to be at least priced comparably to Remicade's net price. [If the price is around Entyvio,] then I do not have any stimulus, I will use this drug for those who fail a TNF-alpha."

US payer

"If the consensus is that they are relatively interchangeable in terms of their efficacy, and we have an opportunity to save money with one over the other, then why not prefer one of them and take advantage of that?"

US payer

ORAL COMPOUNDS MAY STRUGGLE TO ACHIEVE DIFFERENTIATION AGAINST ONE ANOTHER DUE TO THE LACK OF HEAD-TO-HEAD TRIALS

In the absence of head-to-head trials for oral-based products against one another and also against TNF-alpha inhibitors, payers expect it will be difficult to achieve differentiation based on clinical features. Therefore, pricing differences may be the most critical aspects that will determine the placement of these new drugs in the treatment pathway. Payers are understanding that manufacturers are not pursuing head-to-head trials against TNF-alpha inhibitors as the oral compounds will likely lose against more efficacious compounds, while head-to-head trials against one another are impossible as the drugs are still in development. The absence of data, however, means that all three pipeline oral compounds – Xeljanz, filgotinib (Galapagos/Gilead), and ozanimod – may compete for the same space in the treatment algorithm, mostly on price grounds.

"We will rely on the G-BA, and when the G-BA says it is all the same since there is no head-to-head data, it is highly unlikely that we would view it differently."

German physician association payer

"If we had some head-to-head comparisons that would be wonderful, but it does not look like we are going to have those, and in some ways, I do not blame the orals not wanting to go head to head with the injectables because they are probably going to lose that battle, there is nothing in it for the manufacturer to do that. There is a lot in it for us as payers – and the other thing is they cannot go head to head with each other because they are not on the market, and so you cannot get FDA approval to do that. That would be another way that we could pick one or two, but we are not going to have any of that data because it is mechanistically impossible."

US payer

"So, again, we have got some of these arguments already between baricitinib and tofacitinib. You know, one is more specific: one is once daily and one is twice daily [...] I do not think it really makes a difference. [...] I think we will learn more about the JAKs as time goes on, but yes it may be that it is more specific so has a better efficacy than some of the others. But as I say, we just do not have the data or do not know. So, I think it will be watch this space, but the same principles will apply to whichever JAK comes through. If we have data to show that one is better than the other I think that will be interesting, but it will have to be head-to-head data, which is unlikely."

UK regional payer

Indirect comparisons are unlikely to translate into added benefit or preferred positioning

In the absence of head-to-head trials, manufacturers may attempt to submit indirect meta-analysis studies attempting to set the efficacy and safety of oral compounds against comparators, but indirect comparisons are unlikely to impact payer views. This is because indirect comparisons are usually not considered as acceptable as they involve differing endpoints or patient inclusion and exclusion criteria, with most payers having stringent requirements in accepting indirect analyses.

"It depends if it is the same population, so if there are indirect comparisons, as you are aware they are very difficult unless they are absolutely identical patient groups. So, what tends to happen is NICE will say yes to them all, clinicians will have a play with them all because they can, and then they will, based on their clinical practice, have a view if one is slightly more effective than the other.

Usually the populations are very different so it is difficult; in terms of eligibility criteria, entry – it just becomes a minefield, and certainly NICE will be unlikely to do that. They will put them all in the same bucket until we have got any definitive head-to-head data or what usually happens quicker is [we get] clinicians' views."

UK regional payer

"We would have to do an indirect comparison; I mean we do that all the time now so it is not a foreign concept, like I say we have to do that now because we are faced with that challenge every time we have a placebo-controlled option, we have to make an intelligent and informed decision as best as we can."

US payer

"Well, the G-BA, as you know, does not accept indirect comparisons. They want to see head-to-head trials. Without a head-to-head trial you are not superior. You do not get an additional benefit rating and so I think it is lost. They cannot win here much market share without at least a minor additional benefit rating."

German physician association payer

"Maybe a small chance it may provide a proper adjusted indirect comparison, but it is more a theoretical chance because out of about 70 indirect comparisons filed so far in the AMNOG assessments, about 10 were accepted I think, and so the chance is quite low of getting an indirect comparison accepted, and especially if there is no real therapeutic need because there are alternatives, so the willingness to accept that is even lower. I do not think that there is a chance."

German sickness funds payer

OTEZLA'S EXPERIENCE IN DERMATOLOGY COULD PROVIDE THE BEST EXAMPLE FOR HOW ORAL IBD DRUGS WILL FARE

Like oral therapies in UC and CD, Otezla is viewed as less efficacious than first-line TNF-alpha inhibitors, but is considered safer than the biologics, and lessons learned from Otezla's launch in dermatologic indications could prove useful for new oral drugs in IBD. Otezla eventually managed to place itself as an option prior to injectable therapy, with price being key in gaining access for this earlier use, and while Celgene priced Otezla too high in the beginning, major discounts and couponing in the US helped the drug gain traction.

Payers caution, however, that while there are some parallels, the same may not apply to oral therapies in gastroenterology. Limited access to the small number of hospital dermatologists in France who could only prescribe biologics helped to build the case for oral therapies like Otezla in dermatologic indications, as they could be prescribed by community dermatologists. There are, however, no access issues to gastroenterologists in hospitals in France. Additionally, while Otezla is viewed as being less efficacious against all TNF-alpha inhibitors, JAK inhibitors are viewed as slightly more efficacious – comparable to Humira but less so than Remicade. These differences may prove to result in different pricing strategies that did not work for Otezla but that may work for the JAK inhibitors. Datamonitor Healthcare anticipates that manufacturers with oral products could apply some takeaway lessons from the launch of Otezla, but will need to keep in mind the differences between the two disease areas.

"Otezla is not very effective, but people love it, but the company also coupons like crazy, so that is how they are really selling that product, with lots of couponing for patients. We have not [relaxed restrictions], but we have seen it in the market, and I think the rationale is that they are going to use that ahead of a biologic, and then it is potentially a worthwhile exchange, in other words use the low-cost oral instead of using the biologic and moving right to it, you go to the Otezla first. It is more likely patients who were complaining because they wanted to use it, it was inexpensive, maybe they tried a sample and it worked. I think that is really more of a driver than the physician."

US payer

"Everyone thought, 'oh, new innovative treatment, just like a biologic but it is a tablet,' and NICE said, [...] 'look, we do not know where this sits in the pathway, but we have tried to put it in early, middle, and late, and it is not effective in any of those scenarios.' And what they say is it is not cost effective, because they are saying although it is cheaper, the efficacy is falling in the modeling. [...] The perception was that apremilast was [of] particularly poor efficacy. [...] As a result of that, no-one was reimbursing it."

UK local payer

"Celgene wanted [Otezla] at a very high price, and then the price went lower and lower and lower until NICE approved it with a very heavily discounted patient access scheme, but you are right; efficacy is not great, it does not really work that well, so [there has been] relatively low uptake. It is for those patients that would not go on to an injectable.

[Uptake increased] when the NICE TA came out probably. There is a cohort of patients that do not want to go on to injectable [therapy]. We had a few patients that had learning difficulties so injectables was going to be a challenge for those patients, and their disease was not so severe that they needed to go on to a biologic yet. [...] They must have come back, and instead of giving 12.5% probably gave like 40%, you

know?"

UK regional payer

"Apremilast could be a good example, but in some regions – well, in Spain – apremilast has had to do a big discount in order to increase use, because it is like methotrexate, more expensive than methotrexate but its efficacy is quite similar to methotrexate. So, currently the price for apremilast is very low compared to the initial price."

Spanish local payer

"It would depend very much on the price for the access decision because for apremilast it was not just a question of the Transparency Committee, it was also very much the decision of the economic committee to give a price, to give access to dermatologists working in the community, so it is a bit different I would say. There is a bottleneck on access for dermatologists in hospitals in France, so if you can give access to an oral drug, which is somewhat effective with a reasonable safety profile, then it can be initiated in the ambulatory care, in the community, by community dermatologists. We may have, I do not know, 200 academic dermatologists in France, maybe 300 at best, whereas we may have 4,000 dermatologists working in the community, so if you look at the figures of patients suffering from severe psoriasis, maybe not all would be served to go to the hospitals, so that was the reason I think. So, it is a question of management. It is less the case for Crohn's, there are many more gastroenterologists in hospitals, we have wards, we have almost no wards for dermatology."

Former French national payer

PAYERS ARE SKEPTICAL THAT ORAL THERAPIES CAN BRIDGE THE GAP BEFORE BIOLOGICS

The value of oral delivery is not viewed as being critical by payers, especially because the efficacy of pipeline oral products is lower than infliximab, the standard of care. Most payers are looking for medicines that are more effective rather than less effective, as patients who are refractory to TNF-alpha inhibitors have very limited options. Nonetheless, JAK inhibitors are perceived to be as effective as Humira, which could present an advantage over the SC formulation for some patients.

"When the EMA grants approval I have to accept this, but I want to see a clear benefit. I want to see some additional benefit. If not, we would just pay a cheaper price for other competitors that are so far on the market, and the first-line drugs are pretty cheap like MTX and other drugs like corticosteroids. So yes, they can dare to enter this first-line market, but they really have to prove a superiority. [...] I want to see a treatment benefit, a clinical benefit. So just saying we are an oral drug and nothing else is not enough. That would relate to convenience, and we would never pay for convenience. So, when they say: 'we are the same line of therapy like infliximab, but we want to get preferred,' well, then show me that you are superior. But when they are superior that means that infliximab has no future role. I mean, it is a little bit difficult to beat infliximab in terms of efficacy and safety. When they decide, well, we just focus on convenience or things that are not crucial like mode of administration and so on, then it is highly unlikely that we would give them a preferred status or even a higher price."

German physician association payer

"That is quite difficult, because what is interesting around that is the unmet need is almost an oral that could replace some of the first horrible drugs we use right at the beginning: methotrexate and these agents. An oral which sits [at] low efficacy but bridging to the injectable, I think I would struggle with that because by the time you fail steroids and azathioprine and cyclosporine and methotrexate, we need to hit hard. You do not hit with a soft bridge."

UK local payer

However, some payers say there may be limited use for oral compounds in a subset of patients

Some payers look to potential safety advantages with oral therapies for the specific group of patients who present with complications, such as the elderly population or those with contraindications or intolerance to TNF-alpha inhibitors, and for those contraindicated to conventional therapy. Other payers, however, see little value even in the safety advantage, contending that current therapies are safe for most patients, and that use is likely to be reserved for TNF-alpha-failure patients, as was the case for Otezla in psoriasis in Italy.

"I think it would depend very much on how you would define the disease activity. Not just the trial population, but with various methodologies they can write a consensus where if disease activity is mild, you go for drug A, and that is probably sufficient enough. Now, for some patients you may have to start immediately with the biosimilar."

Former French national payer

"Less efficacy could be interesting for mild or moderate patients."

Spanish local payer

"Well, we consider four big items: efficacy, and if there is less efficacy we penalize that kind of treatment; safety, so it is a good point if a new drug is safer than an older one; convenience is another good point; and the whole item's cost. If it is less effective but safer and more convenient, and possibly less costly, it could be important to consider this kind of treatment. Paying more for a less effective treatment is a bit difficult to understand, well, the current treatments are quite safe, we have no real big problems with the current treatments."

Spanish local payer

"Yes. It is that risk-benefit is [...] about getting the right positioning in the pathway, so I do think that there is a role for these molecules, but it may be at a sensible price. Then it is down to clinical decisions for individual patients, because what they have to assess is in terms of a patient benefit and those individual side effects, are they going to be an issue for that individual patient in front of them?

From a commissioning perspective, we would not be guiding anything, and that is down to that clinical input with the patient in front of them, with the risk-benefit of the safety in that patient and the severity of that patient's disease. I think we step out of it at that point and we say: 'yes, you have got these options and this is the pathway,' but it is a clinical decision at that point.

If they are intolerant to immunosuppressants such as azathioprine then they may be able to go straight on to one of [the JAK inhibitors] instead, but if not, I think you would still cycle through the immunomodulators because they are always still going to be so much cheaper. Azathioprine or cyclosporine is going to still be cheaper."

UK regional payer

"I suspect in reality, these older, multi-morbid patients probably do not fall within the evidence data collection of these products. So, there will be some debate about when a physician says: 'oh, I have a 90-year-old who has got liver disease, heart disease, Crohn's disease, ulcerative disease, three different cancers, is dying of TB, let us use this little molecule. It looks very safe,' but you can imagine payers saying: 'you need to stop prescribing for this patient.'"

UK local payer

"[AIFA is] looking at the efficacy, and in this case even without a direct comparison the efficacy is lower than infliximab for this and other types of JAK inhibitors. What I can conclude is that the only chance for this drug to be approved is just in case of patients intolerant to infliximab."

Former Italian national payer

Existing contracts in the US hinder positioning of oral compounds ahead of TNF-alpha inhibitors

Payers in the US are especially concerned that adding oral compounds into the formulary will upset existing contracts with the highly used TNF-alpha inhibitors Humira and Remicade because of their approvals in multiple indications, including rheumatoid arthritis (RA). Payers expect that until Humira and Remicade move towards indication-based contracting, little will change with regard to the present arrangements. Payers have more to lose in upsetting their existing contracts with these drugs, and are not likely to risk taking discounts from oral inhibitors whose therapeutic use reaches far beyond gastroenterology. Datamonitor Healthcare expects that US payers will continue to instate step therapy with Enbrel (etanercept; Amgen/Pfizer/Takeda) and Humira prior to accessing Xeljanz.

"We are still going to go with our core sequencing based on the contracts that we have in place, I just do not see that changing. It is too risky because two or three points of contract loss is millions of dollars, so it is not a few hundred thousand, it is millions, so that is the challenge we face in this whole autoimmune space, and because of the multiple indications, it is not an indication-specific issue, it is across all indications.

We still have our Humira preferred, you still have to step through all the other agents, so I think Xeljanz right now does not have a step through Humira, but we may add that going forward, we have not decided yet. So, that could be a change, but I would think that for this indication we would probably have the step, and again it is not effective either, so that is a concern."

US payer

Physicians look forward to the launch of Xeljanz in UC

Key opinion leaders are expressing enthusiasm regarding Xeljanz's launch. Physicians report that the oral formulation is an asset, and that the efficacy data, especially the sustained remission data, are also an advantage for the JAK inhibitor. Assuming Xeljanz can overcome the existing safety issues experienced in RA, physicians would warmly welcome the launch of the first oral medicine in UC.

"The big asset of this drug is that of course it is an oral drug. So, if the efficacy data are confirmed in Phase III, if the safety profile looks reasonable, I think this will be a big progress in the treatment of UC [...] because it is an oral drug."

EU key opinion leader

"Looking at the Phase II and Phase III trials, I have to say Xeljanz is a very good drug. Nearly 50% of patients achieved remission, and nearly half of these patients were still in remission at year 1."

EU key opinion leader

Payers have varying viewpoints on Xeljanz's efficacy, and are conflicted regarding its consequent positioning

Xeljanz is perceived to have similar efficacy to Humira, and reduced efficacy compared to standard-of-care infliximab, leaving payers struggling to find a consensus with regard to its therapeutic placement. Some are advocating Xeljanz as an early bridging therapy, while others plan to place the drug after TNF-alpha inhibitors or for patients who are contraindicated for or intolerant to TNFs. The

matter is divided between those in support of the step-up approach, involving using compounds that have lower efficacy prior to transitioning to more efficacious biologics, versus those who are in favor of beginning therapy with well-known effective treatments and resorting to less efficacious treatments later. Without conclusive evidence for therapeutic placement, Datamonitor Healthcare anticipates pricing will be the key determinant of Xeljanz's positioning in the therapeutic pathway. Pricing in line with biosimilar infliximab would reduce the risk of payer barriers to access in both UC and RA, where the drug is already approved.

"[Xeljanz] to me is not useful in Crohn's disease at all, it is kind of lukewarm data, yes, you do get 40% – I do not know what that 40% is, is that a percentage of responders, and we are used to drugs for inflammatory bowel disease, especially ulcerative colitis, having fairly low response rates, but to me this does not add anything to Xeljanz. Again, it is a second-line drug for us in RA, and I think it would still be a second-line drug for us in ulcerative colitis. It does not seem to be nearly as attractive as a different mechanism of action like etrolizumab for instance."

US payer

"I think that [Xeljanz] may have a problem. The efficacy that is being painted does not look particularly great, and payers may well evaluate the data and paint an even worse picture. They generally do. What worries me is, you may have a product that even if it is cheaper, an oral may be considered less effective and will not be reimbursed. You know we saw this for plaque psoriasis."

UK regional payer

"Well, I suppose a new indication would have a price reduction, but it is quite complicated if [Xeljanz] has less efficacy than infliximab but is more expensive than infliximab. It is very difficult to justify using a drug before infliximab only because it is oral, that is my opinion, then its space could probably be in second line after infliximab because it is another option to offer to a patient."

Spanish local payer

"Well, I think that in this case, in naïve people, [Xeljanz] does not offer improvement. I think that this drug may be useful in TNF-alpha-failure patients. I think that one question is the survival of this drug. I think that that is very impressive. It impressed me – the survival, the sustained remission at 52 weeks. I think that that is another improvement, and another improvement is the different mechanism of action and the administration route, by oral administration. It is easy to administer. That is an advantage as well."

Spanish regional payer

"I am absolutely sure that AIFA will not be sensitive to a proposal [for bridging] because if the [indirect assessment] shows inferiority to infliximab, the only possibility of approval of this drug is only for those patients who are not treatable with infliximab. But considering that other drugs can be used in those patients, I would conclude that the future of this drug is not really easy."

Former Italian national payer

ACCESS FOR JAK INHIBITORS HINGES ON PRICING STRATEGY

Given the competitiveness of the IBD market, payers expect that positioning for JAK inhibitors will hinge on pricing. Payers say that with a heavily discounted price, it is foreseeable that JAK inhibitors could be used before TNF-alpha inhibitors. At a minimum, JAK inhibitors need to be competitively priced at around the price of TNF-alpha inhibitor biosimilars in order to be a bridge to biologics. Some payers caution, however, that even comparable or slightly reduced pricing compared to TNF-alpha biosimilars may not be enough of a discount, as biosimilar infliximab is the standard of care and is more efficacious than JAK inhibitors. At a price slightly higher than TNF-alpha biosimilars, JAK inhibitors will be placed after TNF-alpha biosimilars, but before branded TNF-alpha biologics. Ultimately, Xeljanz's options may be largely limited by the pricing strategy Eli Lilly decides to pursue for its JAK inhibitor Olumiant

(baricitinib), which beat Xeljanz to market for RA in the EU.

"I would say if they were 50% of the cost on the market [compared to Humira's list price], you know, the companies would be hard pressed to tell us, well, you have to use [biosimilar adalimumab] before [JAK inhibitors]."

US payer

"If it is below the biosimilars, even if it is 10% below the biosimilar, why not have the patient go to an oral agent, you know? That would have been the Otezla strategy, but it did not work for them because they priced it lower but not low enough, and they were less potent, and so payers did not flock as you are well aware in the US to Otezla. [Otezla should have been] less than half the [net price] of the biologics. [...] It is all going to be relative to where the biosimilar is. [...] I think it is probably going to have to be priced similar to the biosimilars, so that we are not paying a huge penalty to move from biosimilar to something else. Maybe if it is 10% higher than biosimilars I am OK with that because they would have already failed a biosimilar, so I am willing to pay something extra. But it has to represent a step between the biosimilars and the branded biologics in terms of cost to the plan."

US payer

"My personal expectation would be the price of JAK inhibitors, regardless of the indication, would be somewhere in the region of the infliximab biosimilar. So, it should go parallel to multiple sclerosis. We had interferons for a couple of years for about 20,000 euros, and then the two or three oral options came to the market and they expanded the market a bit because the patients were willing or there was obviously a need for oral options both for getting rid of the interferon side effects and the initial therapy was at 20,000 euros, the orals came in at 15,000 euros and made a good market. The maximum is parity with no added benefit, but parity to the originator is really unlikely in the scenario where biosimilars are available, and so maybe somewhere between the originator and the final biosimilar price, but more on the biosimilar end. But there is a good market then, because they are oral and if they are safe there will be a market for this drug."

German sickness funds payer

"In my opinion, no [it cannot be used before infliximab even if priced below biosimilar infliximab]. That makes no sense because the traditional way to treat these patients is TNF-alpha, and if a drug is not superior to these TNF-alphas it makes no sense to use it before."

Spanish regional payer

"It is possible [to position prior to a biologic]. They can do so. Then it is OK, but really the price is crucial. Then it is an alternative and the doctor [can] choose it, but certainly not with a higher price than the biosimilar. Because they will not have received a negative benefit rating and therefore as a payer I would be relaxed and I would leave it to the physician and what they think."

German physician association payer

Filgotinib's greatest opportunity for differentiation will be through pricing despite the advantages of a broader evidence base

As a second JAK inhibitor expected to receive approval in an IBD indication, filgotinib will have the option to take market share from Xeljanz through an aggressive pricing strategy. This is likely to be the drug's main opportunity to take market share, even in spite of it having some potential advantages over Xeljanz. The first possible advantage lies in its potential for use in both CD and UC; filgotinib is being tested for CD and for UC, giving the drug a leg up over Xeljanz, which had a disappointing clinical trial in CD. Payers also express positive opinions regarding filgotinib's Phase III DIVERSITY trial in CD patients refractory to TNF-alpha inhibitors and to Entyvio, as this helps to identify therapeutic placement, and would lend greater weight to the efficacy data obtained from a harder-to-treat

population. However, unless substantial differences in efficacy or safety are observed in Phase III trials, pricing will remain the main avenue for differentiation.

"I think [filgotinib would compete with other JAK inhibitors]. So, for doctors it would not make any difference. It is the same. When the price is as cheap as a biosimilar, I would not care, so it is OK. We would reimburse it and that is it."

German physician association payer

"In the absence of head-to-head comparisons, like filgotinib and Xeljanz, nothing will happen differently compared to those two drugs. But, if they are available at the same price, it could be a trigger for the physician, because if there are price constraints he can make his individual safety considerations and prefer one over the other, but [only] at the same price."

German sickness funds payer

"Well, it is always good if you have more indications, but at the end of the day you still have to compete against the big players on the market. So, nice to have, but not necessarily enough that would push it over the top."

US payer

"[The DIVERSITY trial] does [give filgotinib an advantage] because if it is working in those very difficult-to-treat patients then it is pretty good, because certainly when you get to that last line of therapy it is a huge challenge to see improvement in those patients, but again that could work against them because we could position it after vedolizumab because they have got the data. So, it is pros and cons really. You can see both sides. It leaves you with a feeling of, actually, if they can show it works in that group and we use it earlier that has got to be good."

UK regional payer

"Maybe at the very late end, if the G-BA makes such a subgroup: failure on one, two, [or] three different options, which is unlikely from my perception, but if the manufacturer can convince the G-BA to establish such a subgroup it can lead to an added benefit for this small subgroup, but again that price is a weighted average across the whole indication and so it will not change things really in the end."

German sickness funds payer

A BETTER SAFETY PROFILE MATTERS TO PHYSICIANS, BUT IS UNLIKELY TO MOVE THE NEEDLE FROM AN HTA OR PAYER PERSPECTIVE

Payers are not willing to trade in decreased efficacy for increased safety when it comes to oral agents in IBD. While no Phase III data are currently available for ozanimod, should such data demonstrate that the drug is safer but less efficacious than Xeljanz, this will not be seen as an advantage from the payer perspective. Payers do not see this trade-off as beneficial as they would rather prioritize increased efficacy and manage safety concerns as an access measure. They note, however, that the absence of black box warning for ozanimod could be an asset from the physician perspective.

"Well, superiority against old DMARDs such as azathioprine, 6-mercaptopurine, [and] methotrexate would be very nice. I would say if you are in a crowded class we would look at both the clinical and cost effectiveness to define the patient pathway and decide whether or not they should use one of these new oral drugs before or after anti-TNF-alpha, and also instead of the old DMARDs, so it should be stated very clearly for clinicians. In other words, the cycling in France I'm afraid for new branded products is unlikely to be left to the physician's choice, it would be decided by the HTA.

They may say for example you can use two very old DMARDs, or just one, then you can go on the new [oral] product, then you go on a biosimilar. They may also say that it [depends] on your disease activity, if you are between this level and this level of disease activity then you go on DMARDs. [...] They would ask for a kind of consensus, so there would be guidelines set by the national health authority, and those guidelines would be a compromise between the health economists, clinicians, biostatisticians, members of the Transparency Committee, patient advocacy groups, and so on in order to have the right compromise, and it would be evolving guidelines, it will not be set forever, it would be like for a few years, and after if you have new entrants they would update. But for sure, they would need a class evaluation."

Former French national payer

"So from an HTA perspective we generally see the effect of safety does not have a massive translation on cost per QALY. It does not. Efficacy does, survival does, health states – so moving from remission to relapse does, but if something has less rash or something has less TB really that does not change much on a scale. It does not dial much. It does when the physician might be choosing between what is available. That might be true, but that dial will not get them through the HTA pricing and say, look, we are safer. Because safer but less efficacious gets you probably nowhere. So, in theory what you see is generally more efficacious products that have more safety issues will get through, then we want to try and manage the safety issues. Look at what we still use first line for all these patients, the most toxic drugs that we have known: methotrexate, cyclosporine, azathioprine. If safety was a value marker we would have got rid of those a long time ago. They are still the most dangerous drugs that we know and yet none of these new treatments have replaced them first line, none of them. So, when you look at what is the dial of safety in the overall context of HTA, it is a weak translator of value. But I think with clinicians generally what they do is, they opt for those options maybe in elderly, frail people where they want to be conservative."

UK local payer

"What would be most interesting is to have an effective treatment, [and to deal with] safety problems when the safety appears. [...] It is important to know which is the most effective treatment and know what the safety problems are in order to decide starting a treatment for a patient. If we have safety problems, then we can accept reduced efficacy, looking at less effective treatments but with better safety, but we would prefer a more effective treatment for sure. [...] Less efficacy could be interesting for mild or moderate patients."

Spanish local payer

"Well, I would say if the efficacy is not better than [JAK inhibitors], that is already one strike against you, right, because that is what we are really after, we are looking for improvements. So, then it becomes sort of the low-priced option that you could consider in terms of an alternative that could be stepped in front of something else, but again if you are starting off right out of the gate – because most of the newer agents that have launched appear to have better efficacy, things like Taltz and Cosentyx, and some of the other autoimmune drugs that have launched do seem to be offering an advantage."

US payer

"[Ozanimod] looks quite clean and simple. It is really interesting. Just one tablet a day. Take it with the aminosalicylate, potentially as a bridging [therapy], potentially as keeping a longer time before you would need a biologic."

UK local payer

"[Ozanimod] in naïve people does not offer more efficacy than the traditional drugs. Perhaps maybe – well, it is easy administration [...] that is another option for patients who have a fear of injections or patients that do not have enough time. There may be a subgroup of patients that [would] be accepting to use this drug, but not in general. [...] It could maybe be used on moderate patients."

Spanish regional payer

"When the comparator [Xeljanz] has a black box warning, but not this drug, then I would say it is meaningful."

German physician association payer

Ozanimod will need a lower price to position itself as a bridging therapy

Ozanimod may have better prospects of being positioned as a bridging therapy between conventional therapies and biologics than JAK inhibitors due to its lack of safety concerns. Lingering doubts over Xeljanz's safety profile and its black box warning may dampen its prospects. However, ozanimod's pricing will still need to be even lower than that of biosimilar infliximab or adalimumab in order to avoid facing payer barriers regarding access to earlier lines of use.

"Maybe they are going to bridge that gap between DMARDs and biologic. Because they are oral, so it is delaying time before an injectable medication, but then it has got to be priced closer to a DMARD price than a biologic price or somewhere in between, which is probably looking at, I would imagine, a maximum of £2,000 a year. Baricitinib is going to be just over twice that figure I just quoted. We would not be using them if they were not, because they have not got the efficacy. So then again, they would say: is this a patient that is rapidly progressing and I want to get them on a biologic to try and control their long-term disease, or is it a patient who is actually [managing OK] – especially with Crohn's because there are quite different patient profiles in terms of their remission and their flares and it may be, if a patient has only had minimum flares and is managing OK and is compliant with oral therapy, this may be the best option before going to a biologic for that patient, whereas there will be some that you know are not compliant, have got disease – you know the risk of their prognosis is looking worse, so yes, these will be positioned in the pathway before biologics, but it will not mean that the clinician has to cycle through this before moving on to a biologic for every patient, but it will be worth them considering. [We will] try a cheaper oral before you use one that we know works better but is going to cost a lot more."

UK regional payer

"I think, from experience, they cannot price [ozanimod] like a biologic and call it a bridge to biologic. One of the benefits of bridging to biologics is I can keep using tablets which will mean I do not have to use the expensive biological therapies. If you come in with a very expensive tablet at the same price as biologic, then I am not bridging anything. I have now just got a biologic on my hands. If I am paying for a biologic, I want efficacy of a biologic. I do not want a bridge to the biologic. So, bridge to biologic conceptually only works in a value construct when it is bridging both efficacy and price. It does not work if it bridges efficacy but the price is the same as the biologic. The right benchmark [for ozanimod] would be looking at what are the most expensive oral therapies we use in that first-line group before they get to biological treatment and then literally halfway. I would say halfway between the oral treatments and the biosimilar price."

UK local payer

OZANIMOD'S APPROVAL IN UC COULD PROVE PROBLEMATIC FOR APPROVAL IN MS

Ozanimod's development in UC could be an issue when the drug launches in MS, as the price benchmark of the drug in MS is much higher than that in UC. In some geographical markets, launching under the same brand for multiple indications would mean that the drug would need to be priced in line with its cheapest indication, or else risk being excluded from reimbursement for UC. As there is no indication-specific pricing for identical molecules with the same dosing, prices will be negotiated when the second indication is launched.

Payers, however, have cited examples in which manufacturers have launched with two brands for two indications despite having the same dosing to allow for different pricing. Whether Celgene chooses to pursue this strategy with ozanimod may hinge upon the launch of generic fingolimod, which could lessen the gap between the benchmarks for UC drugs and MS drugs, and make pursuing a two-branded strategy more cumbersome than necessary. Datamonitor Healthcare anticipates that the manufacturer could follow the lead of the launch and marketing strategy for similar products such as everolimus, which has been successful in launching separate brands for different indications.

"It would have to be a whole different product that comes in for UC. The branding would have to be different. Usually there are legal things around this. The patient information that is supplied with the products is related to their condition. There are EU regulations about this, so what I would anticipate is ozanimod for UC would be funded and paid for locally by [clinical commissioning groups]. Ozanimod for MS would come out of the NHS specialist commissioning in only specialist centers and a different branding and packaging, probably in theory a different brand name. So even [for] the prescribing physicians, it is a different location, different prescribing.

The price, what could be tricky for them is that at the NICE level we have seen a little bit of precedent-setting where NICE will approve the most cost-effective indication, and every other indication will be reimbursed at that price. So, let us just say you can get 1,000 dollars a dose for MS, but 200 dollars a dose for UC, what NICE would say is everyone gets 200 dollars a dose."

UK local payer

"We have some examples, you can commercialize with different brand names, ie a brand name for one indication, like there is one drug that we have for breast cancer, and the same drug is an immunosuppressant. Afinitor is for breast cancer, Votubia is for brain cancer. Different price, different brand names, at the same dose. There are other examples. With the same brand name it is like a risk-sharing agreement, you pay the full price for multiple sclerosis, and less for colitis, and in time you would give the money back for a different mechanism."

Spanish local payer

"If it has no added benefit in the IBD space, it has a given price in MS which is higher, this will lead to a price drop of the drug. I do not know how much, but it could lead to the situation where it is one of the cheapest in MS in the end and a bit more expensive than the comparators in the IBD space. In this case, we would be happy and do nothing and maybe encourage physicians to use it in MS first, because MS might have a higher budget impact in that time. I am not sure whether it makes a huge difference, but, as I mentioned in the beginning, we manage drugs as a class and not as indications, and we would not start things like please use this drug in MS first, but avoid it in RA. We would try to negotiate a price which fits both indications."

German sickness funds payer

"The legal framework would allow that, but it must be two different brands. An example is nintedanib for idiopathic pulmonary fibrosis, and they have also an oncologic indication and so they have different prices. In IPF it is cheaper than in oncology, so it is possible. Yes, it works, but it must be different [brands], otherwise it is not possible because we have no indication-specific prices for the same package."

German sickness funds payer

"We do not have indication-specific pricing in Germany. Prior to AMNOG that was possible, after AMNOG we would negotiate just one mixed price."

German physician association payer

"This is more complicated to me because ozanimod is going to compete directly with fingolimod in MS, and so we know that the MS drugs have a whole different price point than the inflammatory – more than double. So, is the manufacturer going to be willing to price this to be competitive in the inflammatory bowel disease market, and, if so, then they are giving up a lot of money over on the MS side. So, this one, I do not see any way that they are going to price it competitively with even the branded biologics for inflammatory bowel disease [until generic fingolimod launches].

Generic fingolimod will be a true generic, it is not a biosimilar, not a complex molecule, so that could change the pricing, although as you are probably aware in the US we have had mixed results with the generic for glatiramer [...] but anyway, if we had generic fingolimod, ozanimod might have to come out at a lower price point than most of the other MS agents, otherwise why would anybody use it unless it were superior."

US payer

"We are going to see these molecules having numbers of different indications are we not? We cannot have indication-based pricing in the UK. We can if it is a completely different dose [but since it is not] there is no chance of that one. Sadly, they have no choice and they will end up being extremely cheap in MS if they want any use in UC, is the bottom line. So yes, in terms of examples that have come before, an orphan drug then going into a wider market, the price has to come down and they need to be competitive. [...] Things like omalizumab in respiratory now has the same price in dermatology. You cannot change it. You have to have that one price."

UK local payer

SOME PAYERS MAY ELECT TO CONTRACT FOR SELECTED ORAL INHIBITORS

Given a choice of oral compounds for UC and CD, some payers plan to use contracting to leverage volume. Some are likely to put all of the oral products in one category, regardless of the mechanism of action, with JAK inhibitors competing with sphingosine 1-phosphate (S1P) inhibitors. Others say there is no precedent for combining all products in one bucket, and will likely include each one as long as there is no substantial price difference between them. As long as this holds true, physicians will have the ultimate say for appropriate prescribing. Datamonitor Healthcare anticipates that physicians will use ozanimod earlier in the therapeutic pathway as a bridging therapy, while JAK inhibitors could also be used early in the therapeutic pathway, or as an option for TNF-refractory or TNF-contraindicated patients.

"I think you would probably bucket them all in a class of oral intermediate step agents, meaning an intermediate step between some of the things like corticosteroids and immunosuppressants, and the biologics. [...] We would lump them together and say OK, do we want to contract for a JAK or are we going to contract for an S1P, maybe we will have a couple, one a JAK and one an S1P, maybe this would fit – I just do not think we know enough about these drugs in inflammatory bowel disease yet. But I think what I do know is that I would not have four different classes of non-biologic disease modifiers for inflammatory bowel disease, I would probably put them in the same bucket and pick one or two."

US payer

"[Contracting] is likely because if the drugs are seen as more or less comparable across one major indication, the sick fund is willing to make a preferred brand because it offers the option for a better net price of this drug. [...] I think this is the likeliest option, that it is up to the physicians to choose between those classes. Only if there should be a really significant price difference, a sick fund will start thinking about it, but again we have no clear framework for managing across drug classes and I do not think it is likely, so it is most likely up to the physicians."

German sickness funds payer

"I think if NICE said yes to all of them we would probably put them in a basket saying: 'look, if you have failed everything, you may want to consider one of these.' We will not fund all of them, but the patient may want to try one of these oral therapies and see how they go. Yes, choose one of those. You have been through azathioprine, you have tried two biologics, so pick and give them a go with this if you want to."

UK local payer

VALUE AND EVIDENCE

INSIGHTS AND STRATEGIC RECOMMENDATIONS

- Remission and sustained remission are the key endpoints used to assess the pricing, value, and reimbursement of inflammatory bowel disease (IBD) drugs. The Committee for Medicinal Products for Human Use (CHMP) in the EU has also mandated clinical remission as a key endpoint. Payers still also use clinical response, especially in patients with severe symptoms where remission may not be achievable. Payers further mention quality of life endpoints and Mayo scores for ulcerative colitis (UC), as well as Crohn's Disease Activity Index (CDAI) scores for Crohn's disease (CD), among the most important endpoints. Some payers also mention time to treatment failure or surgery as interesting endpoints, while others want to see evidence on direct medical cost offsets to demonstrate tangible savings.

- Quality of life is important for German and UK payers for technology assessments and evaluations of cost effectiveness. Payers scrutinize the scales and validated questionnaires along with physician input to support patient-reported outcomes. For manufacturers, having robust quality of life data could make the difference between having to concede to patient access schemes and discounts versus obtaining free pricing.

- US and EU physicians and payers want head-to-head trials to directly assess efficacy and determine pricing, and indirect comparisons are unlikely to be sufficient. Clinical trials should be at least six months to a year in duration, and should ideally include extension studies in real-world settings.

REMISSION-BASED ENDPOINTS ARE KEY FOR MOST PAYERS

Payers interviewed by Datamonitor Healthcare state that remission and sustained remission are the most important endpoints to assess when looking at the pricing, value, and reimbursement of UC and CD drugs. Some European payers also report that since the CHMP has mandated clinical remission as a key endpoint, they too are following suit, and have criticized candidates that only have clinical response as a primary endpoint. Clinical response is not entirely dismissed, however, as payers still accept this endpoint when dealing with severe cases where patients may not achieve clinical remission. Payers caution, however, that clinical response should be well defined and validated, and should demonstrate an observable difference for the patient.

Respondents also consider quality of life, as well as Mayo scores for UC and CDAI scores for CD, among the top three most important endpoints. Histological and endoscopic endpoints are not as critical for payers, although they are still necessary for regulators and clinicians. Some payers also see usefulness in these endpoints as confirmation of disease remission.

"The TC in this instance is pretty much aligned with the CHMP. The CHMP has changed their guidelines, and they say to get approval tomorrow you will need to demonstrate a rate of remission at week 6 or 8, and maintenance of remission at week 52, and this should be a primary endpoint, and in addition you should do an endoscopic study for a subset of patients in order to demonstrate the proportion of patients who achieve endoscopic remission at week 52, so that is the key opinion leaders, the clinicians are willing to see that, and therefore the Transparency Committee are quite happy with those endpoints in addition, which means that the Transparency Committee is likely to be more stringent, and to say for the endoscopic study I want to have a well-powered sub-study that demonstrates a difference in endoscopic remission, and not just the description of endoscopic remission. [...] The second thing would most probably be quality of life improvement, when achieving remission it would also be a matter of concern, so a very good [patient-reported outcome] would of course be interesting for the Transparency Committee. The reason is that sometimes you may achieve remission but still have symptoms because of irritable bowel syndrome for example, which is a very prevalent co-morbidity, and sometimes the patient may have let us say almost no symptoms, but still

have some endoscopic lesions, which means that anyway this patient would evolve and would be refractory to your drug despite clinically speaking being a good responder today. So, that is the reason why they focus on those two additional sources of information."

Former French national payer

"Certainly, the remission rate; yes, [sustained remission] would be of great value. Then, I would say the improvement in patient quality of life, and then I would say it is the Mayo score – in that order. More or less the same [for Crohn's disease]. Remission is key, then quality of life, and then I would say the CDAI score. [Histological endpoints] are a surrogate endpoint. [Corticosteroid-free remission is] not a major issue. That is just nice to have, but not a game changer."

German physician association payer

"In the clinical trials the DAI and CDAI were used or are used, but in the clinical setting I think remission and clinical remission. [Sustained remission] is very important because these agents lose activity over time. The drug survival or the persistence of the drug is very important. Complete remission is more used, with variables that have a specific value like CRP [c-reactive protein] or radiological or histological examination. I think those are objective endpoints or objective outcomes that we prefer over the DAI or CDAI. [...] Yes, [PROs or QoL] may be added to these results, but the patient-reported outcomes may be with a validated scale, but may be appreciated also."

Spanish regional payer

"I would put remission, sustained remission, quality of life. We expect to see [endoscopy and mucosal healing endpoints] in the trial, but when it comes to talking about value, pricing, reimbursement, and access, it is remission."

UK local payer

"Well, first of all it is clinical remission, of course sustained remission is considered too, and quality of life, and histologic and endoscopic endpoints [in that order]. [...] Sometimes we do not reach clinical remission because the [severe] patients use all kinds of treatment and they still cannot be controlled, then sometimes you use clinical response as a good parameter. But we look for remission. For [Crohn's disease, it is] more or less the same, but we sometimes use corticosteroid-free remission."

Spanish regional payer

"Well, clearly clinical remission is the most important endpoint for us. The Mayo ones I'm not as familiar with, but clearly remission, clinical response, obviously histologic or endoscopic endpoints would certainly be compelling as well. It would be the same for CD, the remission, the clinical response, certainly the CDAI score improvement because we do have disease activity as the standard recognized validated scale, so that would carry a little bit more weight. [PROs and QoL] we like to have but are not that powerful because we do not typically have a lot of quality of life data, so it is not as though we can compare it to other things."

US payer

"Clinical remission is absolutely the number one that we still discuss. I had in-depth discussions around mucosal healing and Mayo scores and at the end of the day, for me as a commissioner, it is clinical response, clinical remission, sustained remission – again, there is lots of patient inter-variability for that, but the patient-reported outcomes and the quality of life are probably the bits that we would focus on as commissioners rather than some of the histological scores: the CDAI, which again I think the clinicians are more interested in than we are."

UK regional payer

"Response, again, is a bit critical, but what does response mean? With Crohn's from very weak to still weak may not mean anything for the patient, and so, again, what the patient can feel matters. If it refers to such scores there is also always the question whether these scores are

validated and whether there is a clear minimum clinically important difference in these scores established to make us sure that it makes a difference for the patient."

German sickness funds payer

Quality of life is an important endpoint, especially for German and UK payers

Many respondents express the importance of capturing quality of life as a significant endpoint, but German and UK payers believe this is crucial as it aids in the technology assessments of the Federal Joint Committee (G-BA; Gemeinsamer Bundesausschuss) and the National Institute for Health and Care Excellence (NICE). Respondents pay specific attention to the scales used, and validated questionnaires, but also look for physician input to support patient-reported outcomes. Given the challenges of non-indication-specific quality of life measures, which may lack sensitivity to detect patient improvement, and non-validated but indication-specific assessment tests, payers would ideally like to have both submitted as part of the evidence package. For manufacturers, having robust quality of life data could make the difference between having to concede to patient access schemes and discounts versus obtaining free pricing.

"It is patient improvement in quality of life and patient-recorded outcomes, signs and symptoms. Symptoms matter always, and again it is the well-known framework – we do ask the question whether a new intervention improves patient-relevant outcomes, and what patient-relevant is is defined by law. It is mortality, morbidity, and health-related quality of life. [...] Morbidity leads to huge discussions if it is unclear whether a patient feels different at the end of the day. A morbidity marker with clear validity is any marker the patient can feel, and so we are at symptoms, and quality of life by itself is relevant due to the definition of the law."

German sickness funds payer

"[What is lacking] for example [is] quality of life. Still some studies are lacking in those [measures], and we need that. It is essential for HTA. Patient-reported outcomes, we like to see some of those. We like those. It gives a more patient perspective. We want to have validated scores. So, if they are using, for example, an IBD questionnaire with EQ-5D, that is good. The visual analog scale. Sometimes these come and they come with scores I have never seen before and I say: 'well, where did you get this from?' and they have used some weird subgroup of a validated score, but just in an area they want to focus on. [...] I think that what most companies need to do is have both a disease-specific instrument to use for measuring quality of life, and also general functional living [that is] non-disease-specific. That is the way forward, not two of one or two of the other or neither of both."

UK local payer

Time to treatment failure or surgery could be valuable for some payers

While some payers have highlighted that data on outcomes such as a delay in surgical intervention could be seen as valuable given that surgery is generally seen as a last-line treatment, others have highlighted the pitfalls around the ability to define such events and their link to final outcomes. In order for such endpoints to gain traction, a definition of particularly disabling surgical procedures may have to established.

"Surgery is a big endpoint. Time to surgery or the requirement for surgery. Treatment failure – we have not actually got a specific treatment failure here as an endpoint. So, some negative endpoints are very helpful for us, because we do use those. Surgery will stop treatment and it takes a sort of different place, right? So, even to say that X number of patients versus standard of care were less likely to need surgery – that would be a very good endpoint."

UK local payer

"Oh, [delaying time to surgery, that is] a very surrogate endpoint. No, that is ultra-weak. [...] That is highly subjective."

German physician association payer

"Surgery can be a good treatment for some of the patients, surgery is very heterogeneous, it can be a surgery for fistulas, it can be a surgery for the removal of the full gut or partial gut, so it is very difficult to define the relevance of surgery, the size, the type of surgery. So, I think the goal of those treatments is to put patients in remission, it is not to avoid surgery because sometimes you have a good reason to do surgery. Maybe some patients may need a small surgery despite being in remission, and others would not benefit from surgery despite the fact that they are not in remission, but let us say they have quite a mild, partial response, which is stable enough not to go on to surgery. Before biologics were available, I remember many patients were very happy to avoid surgery with azathioprine, but it was just a matter of personal choice by the patients that was not challenged by both the gastroenterologists and surgeons."

Former French national payer

"The aim of this kind of treatment is to control the illness, but avoiding surgery could be the final objective."

Spanish local payer

Evidence on direct medical cost offsets is more tangible

Evidence on a reduction of direct medical costs associated with hospitalizations may be of particular value for agents targeting more severe patients or later lines of therapy, where such events are more common.

"Yes, I mean I think certainly if you can have a surgical cost or medical offset, that would certainly be valuable, something that we would consider, and that is one of the advantages of some of these agents, right, if you are going to prevent somebody from having a surgical resection or some other situation, I mean that is a legitimate saving you can count on."

US payer

"*Sure [hospitalization costs], that would be another one that has that potential. Any medical cost you can avoid in using one of these agents [...] you could compare a control group with a treated group, we factor that in to our evaluation discussion, that in fact it does demonstrate some cost offset savings if you will."*

US payer

KEY OPINION LEADERS AND PAYERS WANT LONGER CLINICAL TRIALS WITH EXTENSION STUDIES

Payers and physicians interviewed by Datamonitor Healthcare state that clinical trials for UC and CD need to be at least six months to a year in duration, and some would like to see extension studies. Payers say that although regulations only require six months, and one-year data are sufficient, two years will lead to greater confidence in the efficacy and safety of the compound. Other payers report that longer Phase III trials are not as important as the extension studies that would allow payers to understand the long-term efficacy and safety after a product has launched.

"The G-BA requires a minimum of six months for chronic diseases, but the golden rule would be the longer, the better. I would say a year is the real minimum, and then two years would be perfect."

German physician association payer

"Well, we would like to see at least a year's worth of data, obviously if you have two years of data it is even more compelling, but 1–2 years is typically normal, you would hope for a range of information."

US payer

"Perhaps one important thing at present is that we must consider that we now have a lot of knowledge with the current drugs, but there is a fear that we do not know [their long-term] efficacy and safety. So, longer studies – not clinical trials, but longer studies with safety information, survival information, tracked survival information would be interesting to support our decisions."

Spanish local payer

US AND EU PAYERS AND PHYSICIANS WANT HEAD-TO-HEAD TRIALS TO DIRECTLY ASSESS EFFICACY AND DETERMINE PRICING

Most interviewed payers and key opinion leaders emphasize the need for head-to-head trials for pipeline drugs to establish comparative efficacy and determine therapeutic positioning and pricing. Although indirect comparisons can be conducted, they are not likely to provide conclusive evidence of superiority during health technology assessments. Further, physicians are not likely to prescribe new drugs over more established candidates unless superior efficacy has been demonstrated, as they tend to be conservative in prescribing new medicines without long-term safety data. However, head-to-head trials themselves are often impossible to conduct for competitors within the same class as they are usually launched at around the same time. Datamonitor Healthcare expects that manufacturers will need to discount products that do not have head-to-head trial data upon launch to promote uptake. To maintain competitiveness and favorable formulary positioning, however, manufacturers need to conduct post-marketing follow-up trials establishing superior efficacy against gold-standard comparators.

US PRICING

Table 4: **US pricing of key marketed IBD drugs, 2017**

Drug	Class	CD annual treatment cost ($)	UC annual treatment cost ($)
Cimzia	TNF-alpha MAb	41,526*	n/a
Entyvio	MAb against alpha-4-beta-7 integrin receptor	33,879	33,930
Humira	TNF-alpha MAb	44,742*	31,928
Remicade	TNF-alpha MAb	24,695*	19,013
Simponi	TNF-alpha MAb	n/a	56,940
Stelara	IL-12/IL-23 inhibitor	97,243	n/a
Tysabri	MAb against alpha-integrin	55,185	n/a

*The US price for Cimzia and Remicade used in the CD patient-based forecast has been lowered by 30%, Humira has been lowered by 40% to account for rebates and discounts. This assumption is based on Datamonitor Healthcare's discussions with key opinion leaders.

CD = Crohn's disease; IL = interleukin; MAb = monoclonal antibody; TNF = tumor necrosis factor; UC = ulcerative colitis

Source: Red Book, 2017

US REIMBURSEMENT

INSIGHTS AND STRATEGIC RECOMMENDATIONS

- Payers consider spend on inflammatory bowel disease (IBD) medications under the single category of inflammatory conditions, with rheumatoid arthritis (RA) accounting for the largest market segment in this category. The level of spend that is attributable to IBD is unclear, but US payers say that it is among the larger indications under the inflammatory category. Spending rises in the category observed over the past few years have arisen mostly from unit cost increases for biologics.

- Inflammatory conditions have comprised the most expensive specialty therapy category for eight consecutive years. Humira (adalimumab; AbbVie/Eisai) continues to lead the inflammatory conditions market, accounting for nearly half of category spend.

- Despite high spending in inflammatory indications, pharmacy benefit managers (PBMs) Express Scripts and CVS Caremark are reluctant to exclude inflammatory class biologics. CVS Caremark has no immunology and inflammatory drugs on its exclusion list for 2018, while Express Scripts also retained its formulary exclusions for 2017 into 2018, excluding Cimzia (certolizumab pegol; UCB/Astellas) for the third consecutive year.

- Prior authorization is the main utilization management tool in IBD biologics within all payer types. Payers utilize both formulary tiers and step therapy to direct the use of preferred brands before accessing non-preferred medications. Entyvio (vedolizumab; Takeda) and Stelara (ustekinumab; Johnson & Johnson/Mitsubishi Tanabe) are most often subject to step therapy with tumor necrosis factor (TNF)-alpha inhibitors, making both drugs the most restricted among IBD biologics. Humira is the least restricted biologic, with a step therapy requirement in only one of the six coverage policies investigated by Datamonitor Healthcare.

- Payers have been looking forward to the launches of biosimilar TNF-alpha inhibitors, but the road to market has been riddled with patent litigation actions. Of five biosimilar TNFs that have been approved in IBD, only two have launched, both of which are biosimilar infliximabs. Biosimilar adalimumab is not expected to be available until 2023 at the earliest.

- None of the TNF-alpha inhibitor biosimilars carry a designation of interchangeability, but Cyltezo is being studied for interchangeability to biosimilar adalimumab in psoriasis. It is unclear if this interchangeability would be extended to gastrointestinal indications, but, if successful, the drug could be the first to be granted pharmacy level substitution without requiring physician consent.

- Payers continue to prefer Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) over biosimilar infliximab in the first year after launch due to dismal discounts. Additionally, payers are currently locked to exclusive contracts for Remicade. Payers say that discounts with a net price difference of 10–25% will be needed for them to switch to the biosimilar as they have to take the additional risk of losing out on lucrative and large-volume contracts for Remicade.

- Payers contract for IBD drugs under one inflammatory conditions category. Drugs such as Remicade and Humira, with approvals in multiple indications, are financially much more attractive as contracting targets for payers. Drugs with narrow indications and approvals in smaller markets, such as Entyvio and Stelara, will continue to be disadvantaged due to payer contract arrangements in this disease category.

- Payers want to carve out the immunology and inflammation segment, but say that IBD drugs are not going to be affected as there are no head-to-head trials in the indication. Etrolizumab's (Roche) launch may instigate category carve-outs for IBD provided it has demonstrable superiority to TNF-alpha inhibitors. As this is the first drug to have an active comparator trial in IBD, strong evidence will bolster the case for indication-specific pricing, as well as allowing etrolizumab to garner market share in

the indication.

MEDICARE PAYS $2.9BN FOR HUMIRA AND REMICADE AT AN AVERAGE OF OVER $25,000 PER BENEFICIARY

The anti-inflammatory drugs Humira and Remicade are ranked among the top 25 drugs with the highest total Medicare drug cost, accounting for $2.9bn in combined cost in 2015. In a released public dataset, the Medicare drug spending dashboard provided a summary of the top 40 Medicare Part B and D drugs with the highest spend (total, per user, and highest increase in cost) in 2015. Humira and Remicade have high total drug costs, but the drugs' usage by beneficiaries is among the lowest, therefore their costs per beneficiary are among the highest, at approximately $21,000 and $29,000 for Remicade and Humira, respectively (CMS, 2016).

Table 5: **Top anti-inflammatory drug prescriptions filled by Medicare beneficiaries participating in Part B and D programs, 2015**

Drug	Coverage type	Overall rank by drug cost	Beneficiaries	Total drug cost	Annual cost per beneficiary	Change in average cost per unit from 2014
Humira and Humira Pen	Part D	11	56,777	$1,662m	$29,278	+22%
Remicade	Part B	19	58,713	$1,242m	$21,170	+6%

Source: CMS, 2016

THE INFLAMMATORY CONDITIONS SEGMENT HAS BEEN THE MOST EXPENSIVE SPECIALTY DRUG CATEGORY FOR EIGHT CONSECUTIVE YEARS

Inflammatory conditions (a subset of the specialty drug category), which includes medicines for IBD, has been the most expensive specialty therapy class for eight years in a row for the large PBM Express Scripts. Additionally, 2016 was the second year in a row in which the specialty category of inflammatory conditions was the most expensive disease category overall, beating the traditional therapy class of diabetes. In 2016, the category's total spend increase was 26.4%, with 11.3% of growth attributed to utilization increase and 15.1% to unit cost increase. The overall growth trend can be partially explained by the utilization increase stemming from higher usage of Humira and newer products such as Otezla (apremilast; Celgene) in other inflammatory conditions outside of IBD, including dermatology and rheumatology, which had a 79.2% increase in usage, in addition to price hikes of individual brands (Express Scripts, 2017b).

The growth trend is expected to continue going forward due to ongoing increases in unit cost and usage, and Express Scripts predicts that the annual growth rate will remain at around 30% until 2019. Biosimilar Humira was approved by the US Food and Drug

Administration in late 2016, but this has done little to mitigate costs as ongoing patent battles have prevented launch (Express Scripts, 2017b).

HUMIRA IS THE DRUG WITH THE HIGHEST SPEND IN THE SPECIALTY CATEGORY FOR ALL EXPRESS SCRIPTS' PAYERS

In 2016, Humira was the drug with the highest spend across the specialty therapy category for Express Scripts' Medicare, Medicaid, and commercial members, capturing a combined 13.4% of specialty drug spend (Express Scripts, 2017b). It is difficult to determine spend for Humira and Enbrel (etanercept; Amgen/Pfizer/Takeda) in IBD specifically, as Express Scripts does not examine drug spending by indication, and most of the spend in inflammatory conditions – the category including both Crohn's disease (CD) and UC – is in RA. According to Express Scripts, Humira garnered nearly half of the market share in the inflammatory conditions market in 2016, followed by Enbrel (which has no gastrointestinal indication), Stelara (approved in late 2016 for CD), and Otezla. Remicade captured only 1.7% of market share (Express Scripts, 2017b).

RISING PER MEMBER PER YEAR SPEND FOR HUMIRA IS MOSTLY DUE TO UNIT COST INCREASES

Total spend on Humira increased from 2015 to 2016 across the commercial sector, with most of this growth fueled by unit cost rises. According to Express Scripts, this can be partially explained by greater utilization of the Humira Pen (Express Scripts, 2017b). This is a minor component, however, as increased utilization is more modest compared to unit cost increases for Humira and Humira Pen; Humira Pen's unit cost in the commercial sector increased by 18% from the previous year (Express Scripts, 2017b).

Datamonitor Healthcare expects that AbbVie will continue to enjoy the latitude to increase costs year on year. Payers seeking to keep price increases in check will have more leverage when Humira biosimilars are launched, likely at a discount to the brand. At that time, AbbVie may need to respond with better offers than biosimilars manufacturers to remain competitive in the inflammatory diseases market.

Table 6: **Specialty drug spend by Express Scripts commercial members (inflammatory diseases market), 2016**

Drug	Rank by spend	Total specialty drug spend (%)	PMPY spend ($)	Utilization change from 2015	Unit cost increase from 2015	Total spend increase from 2015
Humira Pen	1	11.3	45.11	+10.5%	+17.9%	+28.4%
Humira	9	2.1	8.15	+2.8%	+16.0%	+18.8%
Stelara	10	2.0	8.13	+18.2%	+3.7%	+18.2%

PMPY = per member, per year

Source: Express Scripts, 2017b

PBMs Express Scripts and CVS Caremark are hesitant to exclude medicines for inflammatory conditions from their formularies

Express Scripts and CVS Caremark, the two largest PBMs in the US, have not implemented significant formulary exclusion strategies in immunology and inflammation indications, despite the high spend in the specialty drug category. Consistent with the past three years, there will be no immunology and inflammation drugs on the exclusion list for 2018 for CVS Caremark, while Express Scripts has also retained the same formulary exclusion list for 2017 to apply to 2018. For the third consecutive year, Express Scripts will therefore continue to exclude Cimzia. With this decision, Express Scripts continues to carry nine products in preferred status, of which Humira, Remicade, Simponi (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) (100mg), Stelara, and Xeljanz (tofacitinib; Pfizer) have applicability in IBD (Drug Channels, 2017). The high-volume use of Enbrel and Humira also provides these agents with an advantage when it comes to securing preferred formulary positions. Due to their broad number of approved indications, manufacturers are more willing to offer better discounting, which is preferable to being shut out of the market.

The PBMs' reluctance to clamp down on immunology and inflammation conditions, however, is in stark contrast to the exclusion-based practices they have instated in other indications. Since 2012, when CVS Caremark first announced its formulary exclusion list, the number of drug exclusions has increased from 34 to 154 products in 2018. Express Scripts, which started with 48 drug exclusions in 2014, has 159 drug exclusions for its 2018 list (Drug Channels, 2017). The large PBMs, which cover approximately 30 million members each in their national preferred formularies, have great influence in getting manufacturers to agree to discounting (Pink Sheet, 2014). The threat of exclusions may have allowed the PBMs to negotiate deeper discounts that drug manufacturers were willing to concede to in order for their drugs to be remain in the large PBMs' formularies. Datamonitor Healthcare anticipates that more aggressive exclusions will take place in this specialty drug segment when biosimilar TNF-alpha inhibitors launch in the US market.

Table 7: **CVS Caremark and Express Scripts' formulary exclusions for IBD drugs, 2016–18**

	2016	2017	2018
CVS Caremark	n/a	n/a	n/a
Express Scripts	Cimzia, Simponi	Cimzia	Cimzia

Source: Drug Channels, 2015a/b; 2016a/b

COMMERCIAL FORMULARIES VARY IN THEIR TIER POSITIONING FOR IBD DRUGS

Branded biologic medications for IBD are largely included in commercial formularies, but the tier positions in which these drugs are placed vary from payer to payer. Humana's three-tier formulary is the most conservative, with all of its IBD drugs in tier 3 (non-preferred brand). Cigna's three-tier formulary lists two drugs as preferred, while Aetna and UnitedHealthcare have at least three preferred drugs. Simponi, approved for UC only, is found in three of the four formularies investigated by Datamonitor Healthcare, but is only preferred in UnitedHealthcare's formulary. Humira is the brand most likely to be listed as preferred in the four commercial formularies that were investigated. Although Remicade is included in some of the formularies, it is mostly reimbursed through the medical benefit (or Medicare Part B), as it is an intravenous (IV) drug. The drug is preferred in Aetna and Cigna's three-tier formularies. Entyvio, which is also an IV drug, is reimbursed through the medical benefit program and is non-preferred in Aetna's formulary.

"Yes, the only one that is preferred is going to be Humira for the GI indication. So, we have Humira and Enbrel as our two preferred products, obviously, Enbrel does not have any GI indications, but it is still one of our two preferred autoimmune drugs, but if it is a UC or Crohn's indication then you have to use Humira."

US payer

"They are all specialty tier, and our preferred agents are infliximab and adalimumab. Obviously, we have Enbrel as a preferred agent, but it does not treat inflammatory bowel disease. So, that kind of sits there for psoriasis and RA, but those are our three preferred agents: etanercept, adalimumab, and infliximab – well, natalizumab is preferred too because it is out there for MS, so we do not distinguish. But it is not used much at all in inflammatory bowel disease."

US payer

Table 8: **Formulary placement of IBD medications in selected commercial formularies**

Drug	Class	On formulary?	Tier	Prior authorization?	Step therapy?	Quantity limits?
UnitedHealthcare traditional 3 tier formulary						
Cimzia	TNF-alpha MAb	Yes	2	Yes	No	Yes
Entyvio	MAb against alpha-4-beta-7 integrin receptor	No	n/a	n/a	n/a	n/a
Humira	TNF-alpha MAb	Yes	2	Yes	No	Yes
Remicade	TNF-alpha MAb	No	n/a	n/a	n/a	n/a
Simponi	TNF-alpha MAb	Yes	2	Yes	No	Yes
Stelara	IL-12/IL-23 Mab	Yes	2	Yes	No	Yes
Tysabri	MAb against alpha-integrin	No	n/a	n/a	n/a	n/a
Humana Rx3 traditional formulary						
Cimzia	TNF-alpha Mab	Yes	3 (powder not covered)	Yes	No	Yes

Table 8: **Formulary placement of IBD medications in selected commercial formularies**

Entyvio	MAb against alpha-4-beta-7 integrin receptor	No	n/a	n/a	n/a	n/a
Humira	TNF-alpha MAb	Yes	3	Yes	No	Yes
Remicade	TNF-alpha MAb	No	n/a	n/a	n/a	n/a
Simponi	TNF-alpha MAb	Yes	3	Yes	No	Yes
Stelara	IL-12/IL-23 MAb	Yes	3 (130mg dose not covered)	Yes	No	Yes
Tysabri	MAb against alpha-integrin	No	n/a	n/a	n/a	n/a
Aetna 3 tier open formulary						
Cimzia	TNF-alpha MAb	Yes	3	Yes	Yes	No
Entyvio	MAb against alpha-4-beta-7 integrin receptor	Yes	3	Yes	Yes	No
Humira	TNF-alpha MAb	Yes	2	Yes	Yes	No
Remicade	TNF-alpha MAb	Yes	2	Yes	Yes	No

Table 8: **Formulary placement of IBD medications in selected commercial formularies**

Simponi	TNF-alpha MAb	Yes	3	Yes	Yes	No
Stelara	IL-12/IL-23 MAb	Yes	2	Yes	Yes	No
Tysabri	MAb against alpha-integrin	Yes	3	Yes	Yes	No
Cigna 3 tier formulary						
Cimzia	TNF-alpha MAb	Yes	3	Yes	No	No
Entyvio	MAb against alpha-4-beta-7 integrin receptor	No	n/a	n/a	n/a	n/a
Humira	TNF-alpha MAb	Yes	2	Yes	No	No
Remicade	TNF-alpha MAb	Yes	2	No	No	No
Simponi	TNF-alpha MAb	No	n/a	n/a	n/a	n/a
Stelara	IL-12/IL-23 MAb	Yes	3 (130mg dose not covered)	Yes	No	No
Tysabri	MAb against alpha-integrin	No	n/a	n/a	n/a	n/a

Table 8: **Formulary placement of IBD medications in selected commercial formularies**

IL = interleukin; MAb = monoclonal antibody; TNF = tumor necrosis factor

Source: Aetna, 2017a; Cigna, 2017; Humana, 2017a; UnitedHealthcare, 2017a

EXCLUSIONS ARE MORE COMMON WITHIN MEDICARE PART D FORMULARIES THAN IN COMMERCIAL PLANS

Medicare Part D formularies have more exclusions of marketed IBD drugs compared to commercial formularies. Additionally, drugs in this area are listed in specialty tiers (five) or non-preferred brands (four) within the five Medicare formularies that were investigated by Datamonitor Healthcare. Cimzia, Entyvio, and Stelara were not found in any of the five Medicare formularies investigated, while Simponi had variable inclusions among the formularies. Consistent with commercial plans, first-generation anti-TNF-alpha biologics Humira and Remicade were included in all of the Medicare Part D formularies.

Formulary exclusion is more common among more financially conscious payers, who will not include later me-too entrants on their formularies unless they bring significant improvements in clinical outcomes over other therapies. Medicare plans are also slower to make changes to their formularies upon new drug launches. As Medicare's cost-management measures continue to take priority, it is likely that later entrants will be included in Medicare formularies long after their addition to commercial formularies.

Table 9: **Formulary placement of IBD medications in selected Medicare formularies**

Drug	Class	On formulary?	Tier	Prior authorization?	Step therapy?	Quantity limits?
United Healthcare's AARP MedicareRX Preferred						
Cimzia	TNF-alpha MAb	No	n/a	n/a	n/a	n/a
Entyvio	MAb against alpha-4-beta-7 integrin receptor	No	n/a	n/a	n/a	n/a
Humira	TNF-alpha MAb	Yes	5	Yes	No	No
Remicade	TNF-alpha MAb	Yes	5	Yes	No	No
Simponi	TNF-alpha MAb	No	n/a	n/a	n/a	n/a
Stelara	IL-12/IL-23 MAb	No	n/a	n/a	n/a	n/a
Tysabri	MAb against alpha-integrin	Yes	5	Yes	No	No
SilverScript Choice						
Cimzia	TNF-alpha MAb	No	n/a	n/a	n/a	n/a

Table 9: **Formulary placement of IBD medications in selected Medicare formularies**

Entyvio	MAb against alpha-4-beta-7 integrin receptor	No	n/a	n/a	n/a	n/a
Humira	TNF-alpha MAb	Yes	5	Yes	No	Yes (kit and pen)
Remicade	TNF-alpha MAb	Yes	5	Yes	No	No
Simponi	TNF-alpha MAb	No	n/a	n/a	n/a	n/a
Stelara	IL-12/IL-23 MAb	No	n/a	n/a	n/a	n/a
Tysabri	MAb against alpha-integrin	Yes	5	Yes	No	No
Humana Preferred Rx						
Cimzia	TNF-alpha MAb	No	n/a	n/a	n/a	n/a
Entyvio	MAb against alpha-4-beta-7 integrin receptor	No	n/a	n/a	n/a	n/a
Humira	TNF-alpha MAb	Yes	3	Yes	No	Yes
Remicade	TNF-alpha MAb	Yes	5	Yes	No	No

Table 9: **Formulary placement of IBD medications in selected Medicare formularies**

Simponi	TNF-alpha MAb	Yes	5	Yes	No	Yes
Stelara	IL-12/IL-23 MAb	No	n/a	n/a	n/a	n/a
Tysabri	MAb against alpha-integrin	Yes	5	Yes	No	No
Humana Enhanced						
Cimzia	TNF-alpha MAb	No	n/a	n/a	n/a	n/a
Entyvio	MAb against alpha-4-beta-7 integrin receptor	No	n/a	n/a	n/a	n/a
Humira	TNF-alpha MAb	Yes	3	Yes	No	Yes
Remicade	TNF-alpha MAb	Yes	5	Yes	No	No
Simponi	TNF-alpha MAb	Yes	5	Yes	No	Yes
Stelara	IL-12/IL-23 MAb	No	n/a	n/a	n/a	n/a
Tysabri	MAb against alpha-integrin	Yes	5	Yes	No	No

Table 9: **Formulary placement of IBD medications in selected Medicare formularies**

UnitedHealthcare's AARP MedicareRx Saver Plus						
Cimzia	TNF-alpha MAb	No	n/a	n/a	n/a	n/a
Entyvio	MAb against alpha-4-beta-7 integrin receptor	No	n/a	n/a	n/a	n/a
Humira	TNF-alpha MAb	Yes	5	Yes	No	No
Remicade	TNF-alpha MAb	Yes	5	Yes	No	No
Simponi	TNF-alpha MAb	No	n/a	n/a	n/a	n/a
Stelara	IL-12/IL-23 MAb	No	n/a	n/a	n/a	n/a
Tysabri	MAb against alpha-integrin	Yes	5	Yes	No	No
IL = interleukin; MAb = monoclonal antibody; TNF = tumor necrosis factor						

Source: AARP, 2017a/b; Humana, 2017a; SilverScript, 2017

MEDICARE PART D COVERS FIRST-GENERATION BIOLOGICS, BUT WITH HIGH OUT-OF-POCKET COSTS FOR MEMBERS

In an analysis performed across all 2014 Medicare Part D and Medicare Advantage plans, HealthPocket found that most Medicare drug plans cover the top 10 drugs (by US sales), including Humira and Remicade (HealthPocket, 2015). These plans, however, have high average out-of-pocket obligations for the patient.

HealthPocket's findings are consistent with the financial responsibilities of the patient in the Medicare formularies that were investigated by Datamonitor Healthcare. Medicare formularies instate steep out-of-pocket co-insurance costs for specialty drugs of around 25–33% of the total drug cost. Humira has increased in price by nearly 20% each year, as evidenced by the Express Scripts Drug Trend report, creating issues with affordability as patients incur co-pays, the variability of which is dependent on the cost of the drug (Express Scripts, 2017b).

Table 10: **Selected formulary practices of top 10 Medicare Part D and Medicare Advantage IBD drugs**

Rank (by US sales)	Drug	Formularies covering the drug	Average out-of-pocket obligations	Formularies requiring prior authorization	Formularies requiring step therapy	Formularies requiring quantity limits
3	Humira	99%	$1,395 (co-insurance fee of 28% of drug cost)	92%	0%	52%
8	Remicade	100%	$1,005 (co-insurance fee of 28% of drug cost)	93%	0%	0%

Source: HealthPocket, 2015

STATE MEDICAID PROGRAMS ARE LARGELY IN CONSENSUS ON THEIR IBD PREFERRED DRUG FORMULARY LISTS

Datamonitor Healthcare analyzed state Medicaid preferred drug lists (PDLs) in New York, Pennsylvania, Texas, Colorado, and Florida. The five Medicaid programs had similar drug lists, with established RA market leader Humira listed as the preferred drug in all five formularies. The formularies were conservative, listing only two or three TNF-alpha inhibitors (excluding Enbrel, which has no gastrointestinal indication) in their PDLs, and regarding the rest as non-preferred. Stelara is universally non-preferred, and Entyvio is only found in Pennsylvania's Medicaid formulary. IV drugs Remicade, Tysabri (natalizumab; Biogen), and Entyvio were either not found in the formularies or were non-preferred.

Table 11: **Formulary placement of IBD medications in selected state Medicaid formularies**

	New York		Pennsylvania		Texas		Colorado		Florida
Class	Preferred	Not preferred	Preferred	Not preferred	Preferred	Not preferred	Preferred	Not preferred	Preferred
TNF-alpha inhibitor	Humira	Cimzia, Simponi	Humira	Cimzia, Remicade, Simponi	Humira	Cimzia, Simponi	Humira	Cimzia, Simponi	Humira
IL MAb	n/a	Stelara	n/a	Stelara	n/a	Stelara	n/a	Stelara	n/a
Integrin MAb	n/a	n/a	n/a	Entyvio	n/a	n/a	n/a	n/a	n/a
Not listed	Entyvio, Remicade, Tysabri		Tysabri		Entyvio, Remicade, Tysabri		Entyvio, Remicade, Tysabri		n/a
Florida only has a preferred drug list. All drugs not on the preferred list are assumed to be non-preferred and will require treatment authorization requests. IBD drugs not on the preferred list include the TNF-alpha inhibitors Cimzia, Remicade, and Simponi, and others such as Stelara, Entyvio, and Tysabri.									
IL = interleukin; MAb = monoclonal antibody; TNF = tumor necrosis factor									

Source: Agency for Health Care Administration, 2017; Colorado Department of Health Care Policy and Financing, 2017; Health and Human Services Commission, 2017; New York State Medicaid Fee-For-Service Pharmacy Programs, 2017; Pennsylvania Department of Human Services, 2017; Texas Health and Human Services, 2017

PRIOR AUTHORIZATION IS THE KEY UTILIZATION MANAGEMENT TOOL USED IN IBD FOR ALL PAYERS IN THE US

Prior authorization is the primary utilization management mechanism used by commercial plans, Medicare drug plans, and Medicaid formularies investigated by Datamonitor Healthcare for all marketed IBD drugs. Prior authorization, or pre-certification, is an extra step that insurance companies can require to decide whether to reimburse a medicine. To obtain prior authorization, physicians have to submit evidence that the patient fulfills the criteria that the insurance plan has in place for the drug to be reimbursed.

Payers use prior authorization to ensure that drugs are used appropriately and in accordance with approved label indications. Drugs for IBD have separate approval labels for UC and CD, and often have labels allowing for multiple indications involved in dermatology or rheumatology. As drug formularies in the US do not specify indications for use, without prior authorization physicians could prescribe these medications off-label, which would incur higher costs and may result in reimbursement denials during claims processing. Although prior authorization presents an administrative barrier in access to treatments, gastroenterologists are used to handling these processes, as all biologics are subject to this requirement. Therefore, it is the specific drug criteria implemented by payers for each drug rather than the prior authorization process that are most relevant in understanding the differences between ease of access to individual agents.

Table 12: **Prior authorization criteria for Crohn's disease drugs with major health insurers and pharmacy benefit managers**

Health insurer/brand	Prior authorization criteria	Step therapy with biologics
Cimzia		
Aetna	FDA label	Two preferred alternatives (one-month trial each for Humira and Remicade)
Anthem	Humira can be used to reduce signs or symptoms, or induce or maintain clinical remission. Preferred biologics must be used unless they are not FDA-approved and do not have an accepted off-label use for UC and Cimzia does, or preferred agents cannot be used due to clinical conditions (eg hypersensitivity to preferred agents, age, pregnancy, serious infections, or concurrent sepsis)	Two preferred biologic agents (Humira, Remicade, and/or Stelara)
CVS Caremark	FDA label	n/a
Humana	FDA label	Humira
Express Scripts Value PDP/UnitedHealthcare Medicare Preferred PDP	n/a	n/a
Entyvio		
Aetna	FDA label	Two preferred alternatives (one-month trial each with Humira, Remicade, and/or Stelara)
Anthem	Allowed for pediatric use (children at least six years of age). Entyvio can be used to reduce signs or symptoms, or induce or maintain clinical remission. Trial with preferred agents can be omitted if patient is unsuitable (has demyelinating disease, or heart failure with documented left ventricular dysfunction or malignancy [excluding superficial skin cancers])	One preferred biologic (Humira, Remicade, or Stelara)
CVS Caremark	FDA label	n/a
Humana	FDA label	Remicade or Cimzia

Table 12: **Prior authorization criteria for Crohn's disease drugs with major health insurers and pharmacy benefit managers**

Express Scripts Value PDP/UnitedHealthcare Medicare Preferred PDP	n/a	n/a
Humira		
Aetna	Per FDA label, and can be used for patients with extraintestinal manifestations of CD (eg arthritis, oral aphthous ulcers, episcleritis, erythema nodosum)	n/a
Anthem	FDA label. Humira can be used to reduce signs or symptoms, or induce or maintain clinical remission	n/a
CVS Caremark	FDA label	n/a
Express Scripts Value PDP	Gastroenterologist prescribing or consult required. Patient is on or has tried, or is contraindicated to, CSs, or patient has tried one agent for CD, or patient has had ileocolonic resection or enterocutaneous (perianal or abdominal) or rectovaginal fistulas	n/a
Humana	FDA label	n/a
UnitedHealthcare Medicare Preferred PDP	FDA label. Prescribing or consult with gastroenterologist	n/a
Remicade		
Aetna	Permitted for pediatric patients (at least six years old) with fistulizing CD (minimum of three months)	n/a
Anthem	FDA label	n/a
CVS Caremark	Pediatric patients – CD can be active or in remission. Up to date with vaccines before initiation	n/a
Express Scripts Value PDP	Gastroenterologist prescribing or consult required. Pediatric patients: approved if patient is on or failed or is contraindicated to CSs or has tried any one agent for CD, or if the patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas, or if the patient has had ileocolonic resection	Adults: Humira or Cimzia
Humana	FDA label	n/a

Table 12: **Prior authorization criteria for Crohn's disease drugs with major health insurers and pharmacy benefit managers**

UnitedHealthcare Medicare Preferred PDP	Prescribing or consult with gastroenterologist	n/a
Stelara		
Aetna	FDA label	n/a
Anthem	FDA label. Used to reduce signs or symptoms, or induce or maintain clinical response or remission	n/a
CVS Caremark	FDA label	n/a
Express Scripts Value PDP	n/a	n/a
Humana	FDA label	Humira
UnitedHealthcare Medicare Preferred PDP	n/a	TNF-alpha inhibitor per FDA label

CD = Crohn's disease; CS = corticosteroid; FDA = US Food and Drug Administration; UC = ulcerative colitis

Source: Aetna, 2017b; Anthem, 2017; CVS Caremark, 2017; Express Scripts, 2017a; Humana, 2017b; UnitedHealthcare, 2017b

Table 13: **Prior authorization criteria for ulcerative colitis drugs with major health insurers and pharmacy benefit managers**

Health insurer/brand	Prior authorization criteria	Step therapy with biologics
Entyvio		
Aetna	FDA label and adults hospitalized with fulminant (severe) UC. Patient meets all of the following: refractory to or requires continuous immunosuppression with corticosteroids (eg methylprednisolone, prednisone) at a dose equivalent to prednisone 40–60mg/day for 30 days (oral therapy) or 10 days (IV therapy); and contraindicated, intolerant, or refractory to 5-ASA (eg balsalazide, mesalamine, sulfasalazine) and immunosuppressants (eg AZA, 6-MP)	Two preferred alternatives (one-month trial each) for UC (ie Humira and Remicade)
Anthem	Allowed for pediatric use (children at least six years of age). Entyvio can be used to reduce signs or symptoms, or induce or maintain clinical remission	One preferred biologic (Humira, Remicade, or Stelara)
CVS Caremark	FDA label	n/a
Humana	FDA label	Remicade
Express Scripts Value PDP/UnitedHealthcare Medicare Preferred PDP	n/a	n/a
Humira		

Table 13: **Prior authorization criteria for ulcerative colitis drugs with major health insurers and pharmacy benefit managers**

Aetna	FDA label and adults hospitalized with fulminant (severe) UC. Patient meets all of the following: refractory to or requires continuous immunosuppression with corticosteroids (eg methylprednisolone, prednisone) at a dose equivalent to prednisone 40–60mg/day for 30 days (oral therapy) or 10 days (IV therapy); and contraindicated, intolerant, or refractory to 5-ASA (eg balsalazide, mesalamine, sulfasalazine) and immunosuppressants (eg AZA, 6-MP)	n/a
Anthem	FDA label	Infliximab or infliximab-dyyb
CVS Caremark	Can be used in adolescents (at least 12 years old)	n/a
Express Scripts Value PDP	Conventional therapy for two months or is intolerant to an agent, or if patient has pouchitis and has tried therapy with an antibiotic, probiotic, corticosteroid enema, or mesalamine (Rowasa) enema	n/a
Humana	FDA label	n/a
UnitedHealthcare Medicare Preferred PDP	FDA label	n/a
Remicade		
Aetna	FDA label and patients hospitalized with fulminant (severe) UC. Patient meets all of the following: refractory to or requires continuous immunosuppression with corticosteroids (eg methylprednisolone, prednisone) at a dose equivalent to prednisone 40–60mg/day for 30 days (oral therapy) or 10 days (IV therapy); and contraindicated, intolerant, or refractory to 5-ASA (eg balsalazide, mesalamine, sulfasalazine) and immunosuppressants (eg AZA, 6-MP)	Two preferred alternatives (one-month trial each) for UC (ie Humira and Remicade)

Table 13: **Prior authorization criteria for ulcerative colitis drugs with major health insurers and pharmacy benefit managers**

Anthem	FDA label	n/a
CVS Caremark	Pediatric patients: up to date with vaccines before initiation	n/a
Express Scripts Value PDP	Gastroenterologist prescribing or consult required. Two months of systemic therapy (CS, 6-MP, AZA, cyclosporine A, or tacrolimus) unless intolerant, or if patient has pouchitis and has tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema	n/a
Humana	FDA label	n/a
UnitedHealthcare Medicare Preferred PDP	Prescribing or consult with gastroenterologist	n/a
Simponi		
Aetna	FDA label and adults with active UC who are hospitalized with fulminant (severe) UC. Patient meets all of the following: refractory to or requires continuous immunosuppression with corticosteroids (eg methylprednisolone, prednisone) at a dose equivalent to prednisone 40–60mg/day for 30 days (oral therapy) or 10 days (IV therapy); and contraindicated, intolerant, or refractory to 5-ASA (eg balsalazide, mesalamine, sulfasalazine) and immunosuppressants (eg AZA, 6-MP)	Two preferred alternatives (one-month trial each) for UC (ie Humira and Remicade)
Anthem	FDA label	n/a
CVS Caremark	FDA label	n/a
Humana	FDA label	n/a

Table 13: **Prior authorization criteria for ulcerative colitis drugs with major health insurers and pharmacy benefit managers**

Express Scripts Value PDP/UnitedHealthcare Medicare Preferred PDP	n/a	n/a

5-ASA = aminosalicylates; 6-MP = mercaptopurine; AZA = azathioprine; CS = corticosteroid; FDA = US Food and Drug Administration; IV = intravenous; UC = ulcerative colitis

Source: Aetna, 2017b; Anthem, 2017; CVS Caremark, 2017; Express Scripts, 2017a; Humana, 2017b; UnitedHealthcare, 2017b

Entyvio, Cimzia, and Stelara are most often subjected to step therapy restrictions

In addition to prior authorization, payers Aetna, Anthem, and Humana utilize step therapy more often compared to CVS Caremark, Express Scripts, and UnitedHealthcare. Step therapy promotes the use of preferred products prior to accessing non-preferred brands, and ensures that physicians explore contracted, less expensive products before moving on to higher-cost medicines. Payers' step therapy requirements and the preferred products vary widely, with some payers requiring failure with one of the preferred products, while others require failure with at least two or three contracted products prior to accessing a non-preferred product. Entyvio, Cimzia, and Stelara require step therapy with TNF-alpha inhibitors in three of the six coverage policies, making the drugs the most restricted among IBD biologics. Consistent with formulary findings, Humira is the least restricted biologic, with a step therapy requirement in only one of the six coverage policies investigated by Datamonitor Healthcare.

DRUGS WITH APPROVALS IN MULTIPLE INFLAMMATORY INDICATIONS ARE FAVORED IN PAYER CONTRACTING

The success of market leaders Humira and Remicade in IBD has been partially due to their ability to garner multiple approved indications in related markets, including RA, which is the largest inflammatory segment. The drugs are also approved in psoriasis, psoriatic arthritis, and ankylosing spondylitis, while Humira is also approved for juvenile idiopathic arthritis and hidradenitis suppurativa. Payer contracts for these drugs fall under the scope of inflammatory conditions, and the large market shares of Humira and Remicade, along with long-term physician and patient experience, give the early-generation TNF-alpha inhibitors an advantage in securing payer contracts over later entrants. This is because even smaller discounts from such high-use drugs can provide payers with more significant savings compared with larger discounts on drugs with lower overall use. Consequently, later entrants are often subjected to step therapy requirements, with patient access occurring only after failure with one or two preferred agents.

"We are still going to go with our core sequencing based on the contracts that we have in place, I just do not see that changing. It is too risky because two or three points of contract loss is millions of dollars, so it is not a few hundred thousand, it is millions, so that is the challenge we face in this whole autoimmune space, and because of the multiple indications, it is not an indication-specific issue, it is across all indications."

US payer

Payers still plan to split inflammatory conditions into smaller segments, but this strategy will likely benefit indications outside of IBD

Payers interviewed by Datamonitor Healthcare are still keen on carving out the immunology and inflammation segment, but this practice is not likely to greatly affect drugs in IBD, as the currently marketed non-TNF-alpha inhibitors do not have any head-to-head trials in this indication, as have been performed in other indications. Datamonitor Healthcare anticipates that indication carving will not be prominent until biosimilar entry, especially for Humira as payers' contracts are heavily tied to the drug.

"I think psoriasis is a classic one, with all of the drugs targeting all the various interleukin pathways, and they are highly effective in their narrow spectrum. So, I suspect – and we are certainly talking about it – that in the future we will probably break up the category into dermatology, arthritis, and inflammatory bowel disease, and consider having preferred agents in each of these subgroups, but we are not there yet. [...] Where it is probably going to be first is in psoriasis, where I think we know that the drugs that target interleukins, whether that be golimumab or secukinumab, or any of those – you know, they seem to be a bit more effective than first-generation drugs. So, they will probably be the ones to benefit first. [...] Because [although] they have not done head to head with every drug, but they have certainly done head to head with some drugs that are considered standards of care. [...] RA would be the next to benefit, and I suspect that the inflammatory

bowel disease category will be the last to benefit unless new agents clearly show that head to head they are better than existing drugs, and I really mean that, it is not comparing across trials, are you willing to do a head-to-head trial against adalimumab, and show you are better, or infliximab. My gut [feeling] is that these drugs are not nearly as effective in the inflammatory bowel diseases as they are in psoriasis; it is a lower response rate, and very often these patients have more relapses and that sort of thing."

US payer

"I think it is possible, but we would have to have some biosimilars on the market before that would happen. I do not see that happening today because Humira, Enbrel, and Remicade have too much market share for us to ignore. Well, right now it looks like maybe the end of 2018 that we might see a biosimilar, so maybe 2019. I think we will just swap out the adalimumab for the Humira."

US payer

The launch of etrolizumab may drive category carve-outs if it proves superiority to TNF-alpha inhibitors

The launch of etrolizumab may make the carving-out of gastroenterology indications more likely if it proves to be more efficacious than Remicade and Humira. Etrolizumab will be the first drug to have an active comparator trial against infliximab and adalimumab, and assuming there is clear superiority against the TNF-alpha inhibitors, it will be the first in an armament of non-TNF-alpha inhibitor compounds that will have demonstrable superiority to anti-TNF-alpha drugs. Datamonitor Healthcare anticipates that this will further bolster the case for indication-specific pricing, allowing etrolizumab to garner market share within the IBD market.

"It is attractive to have a drug that specifically targets inflammatory bowel disease, and if indeed it is superior to infliximab and maybe even superior to adalimumab, you know that might be a stimulus to really create a separate category, but again we are going to have the same issues that we have been having with psoriasis. We certainly feel there is superiority to the agents that target the interleukin pathways, but the problem is that we have not been able to create that category because of the contracting issues. But I think where we are getting is that maybe there will be enough agents specific to each of the different subgroups that eventually we can move to that. So, it is an attractive agent."

US payer

FIVE TNF-ALPHA INHIBITOR BIOSIMILARS HAVE BEEN APPROVED BY THE FDA, BUT ONLY TWO HAVE LAUNCHED

Only two of the five FDA-approved TNF-alpha inhibitor biosimilars have launched to date due to ongoing patent litigation issues. The three first-generation TNF-alpha inhibitors – Enbrel, Humira, and Remicade – each face impending competition, as the FDA has approved biosimilar counterparts for each brand. Enbrel does not have an indication for IBD, and so will not impact the market in gastroenterology. For the time being, only Remicade biosimilars Renflexis (infliximab-abda; Merck Sharp & Dohme/Samsung Bioepis) and Inflectra (infliximab-dyyb; Pfizer/Celltrion) have launched (Pink Sheet, 2017a). Ixifi (infliximab-qbtx; Pfizer), the third biosimilar approved, is not expected to launch as Pfizer is fully committed to marketing Inflectra in the US (Pink Sheet, 2017b). Both Renflexis and Inflectra were launched at-risk amid ongoing patent litigation; however, Johnson & Johnson dropped the lawsuit for Renflexis in November 2017, but a suit still stands for Inflectra (Scrip, 2017). Nonetheless, the at-risk launch was a first among approved biosimilars, and may attest to the confidence, ever-changing landscape, and increasing market acceptability of biosimilars.

Humira's biosimilars may be facing a different fate, however. Amgen reached a settlement with AbbVie in September 2017 to delay the US launch of Amjevita (adalimumab-atto; Amgen) until 31 January 2023. It remains to be seen if Cyltezo (adalimumab-adbm;

Boehringer Ingelheim) will face the same fate as Amjevita, but Datamonitor Healthcare expects that the ongoing patent litigations with branded TNF-alpha inhibitors will continue to delay the availability of adalimumab biosimilars in the US, as most manufacturers are not likely to choose an at-risk launch strategy.

TNF-alpha inhibitor biosimilars are not approved for interchangeability

All five approved TNF-alpha inhibitors carry the biosimilar labeling of four suffixes after the active ingredient, designating the products as biosimilars to Remicade or Humira; however, they do not have an interchangeability designation. Indeed, no interchangeable biosimilars have been approved so far, despite the FDA's release of biosimilar interchangeability guidance in January 2017 (FDA, 2017). The lack of interchangeability status is not a significant factor that will impact uptake of IV administered biosimilars like Remicade, as it is administered in physicians' offices; however, for future biosimilars of Humira, interchangeability designation is likely to be a more important factor.

Boehringer Ingelheim has set out to prove the interchangeability of its biosimilar adalimumab to Humira in psoriasis

Boehringer Ingelheim has initiated the first clinical study on interchangeability for its TNF-alpha biosimilar Cyltezo in the US, for the psoriasis indication. The VOLTAIRE-X clinical trial intends to compare clinical outcomes and pharmacokinetics in a head-to-head trial against Humira and to assess safety, immunogenicity, and efficacy (Boehringer Ingelheim, 2017). Results are currently still awaited as Boehringer Ingelheim only started enrollment in July 2017. Further, with particular regard to the IBD market, it is unclear if interchangeability would then be extrapolated to gastrointestinal indications. If the manufacturer is able to attain an interchangeability designation, this would be the first biosimilar capable of pharmacy level substitution without a physician's consent. Although this ruling is still dependent on the state, more than half of all US states are considering or have passed laws on the substitution of biologics. An interchangeability designation that is extrapolated to gastrointestinal indications could further threaten Humira's market share in the US.

PAYERS CONTINUE TO PREFER REMICADE OVER BIOSIMILAR INFLIXIMAB

Inflectra, the first biosimilar infliximab launched in the US, has not had much market success in its first year on the market, as manufacturer Hospira did not engage payers in discounts. Payers find themselves currently locked to contracts with attractive discounts for Remicade, although many are up for negotiation. Despite an opening window to switch allegiance to biosimilar infliximab, some payers are concerned that in preferring the biosimilar, they will lose out on the existing contract prices for the majority of new patients who are still on Remicade.

"Right now, we have a contract on Remicade; we do not save anything with the biosimilar. The biosimilar is available and if physicians and patients choose to use it, we have not stopped it, but we are not promoting the biosimilar at this point.

One of the problems that you run into is you have this large mass of patients who were on Remicade, many of them will not be switched off Remicade because I do not think physicians are comfortable switching. They will start new patients on biosimilars more readily than switching. So, now if I re-contract either my rebate goes down or even goes away because I prefer the biosimilar, [and] I am going to be in a huge cost hole until I can convert a big piece of the market, which could take years with a biosimilar. So, we are at a bit of a dilemma here, you know biosimilars are attractive, but because we have been enticed by the lure of preferred drug contracting and rebates, we are bit locked into our current Remicade contract, [so] it is going to be hard to take it away."

US payer

"There was no change because the biosimilar launched at a 15% discount, but the ASP discount for Remicade was 30% below, so there was no financial benefit to that new drug. As of 1 July, we finally saw a discount appear in ASP for Inflectra, but prior to that the price and the ASP price were identical, and now the ASP for Inflectra is actually below the ASP for Remicade. So, for now at least, it makes it more attractive from a pricing perspective. [...] ASP actually reflects the discounts given to purchases in the marketplace, not wholesale. So, this would be physicians, infusion centers, home infusion companies, so anybody who was buying Inflectra at a discount, that is what rolls into that ASP pricing calculation."

US payer

LARGER DISCOUNTS ARE REQUIRED TO PROMOTE BIOSIMILAR INFLIXIMAB USE

Payers comment that discounts observed with biosimilar infliximab to date have not been sufficiently high to warrant more aggressive strategies to promote biosimilar use. Payers are expecting a net price difference of 10–25% for them to act on this strategy, and companies that launch further biosimilar infliximab products can capture better coverage among US payers if they are willing to discount more aggressively.

"What it will come down to is how big a discount will Janssen offer, and how much pushback you expect to get from providers if you try to block the Remicade. So, again, maybe Janssen comes in and says so right now they are about 30% less expensive for us just by what we are paying on ASP, now you have set Remsima as 35% off the WAC. So, Janssen came in and said listen, we will give you 15% rebate, and that puts us at 10% advantage over Remsima. If we can save 10% on our Remicade business, I mean that is probably worth a couple of million bucks."

US payer

"Certainly the net price of the biosimilar would have to be substantially lower than the net price of Remicade, maybe 20–25% even, otherwise it is going to take us forever if we can ever dig ourselves out of that hole we will get [into] by either losing or having a profound reduction in our contracting concession."

US payer

Some payers will elect to use co-pay differentials to push for biosimilar adalimumab's uptake

Payers anticipate that sizable uptake of biosimilar adalimumab will require different strategies compared to infliximab as the drug falls on the pharmacy side and is subject to contracting. Payers usually resort to step edits, placing products with favorable contracting arrangements in preferred positions. However, some payers are also planning to instate greater co-pay differentials between the preferred biosimilar product and the non-preferred branded product to promote uptake. This process relieves the need for payers to aggressively ask for discounts from manufacturers, and instead places the decision in the hands of the patients. Datamonitor Healthcare anticipates that with increasing co-pay differentials, many patients will opt to self-select for more cost-effective options.

"There will be co-pay differentials that will drive preferred status, as well as using step through preferred drugs, and patients will have an incentive aligned with using the preferred drug. [...] It will not be in 2018 for most of us because if that were going to be the case we would already be well down the pathway of having those benefit designs in place. 2019, and even 2020, for a lot of plans is probably not unreasonable. This is speculative because it is not here, [...] a preferred biosimilar or a biosimilar category that patients would have an incentive for, and then we could still have some preferred brands out there. So, I do not know that I am expecting the brands to be priced like the biosimilars necessarily, but recognize that say it is $100 a month out of pocket for a biosimilar versus 25% for a brand, patients and doctors are probably going to flock to the biosimilars. So, I think just like what we have done in small molecules, you let the market speak for

itself, right? The patients just started using generics when they realized it was a lot less expensive."

US payer

Manufacturers' coupons may disrupt utilization strategies

Payers planning to instate co-pay differentials state that manufacturer coupons could threaten their utilization strategies by allowing patients to skip the step-edit requirements. Manufacturer coupons absolve the responsibility of the patient to make a co-pay, thereby nullifying payer utilization strategies. Some payers plan to counter this threat by switching all patients to biosimilar adalimumab when the drug launches, and not allowing Humira to continue. Datamonitor Healthcare anticipates that payers could resort to formulary exclusions if biosimilar uptake strategies are hindered by AbbVie.

"We have a very favorable contract with adalimumab [Humira], and if you think about it adalimumab has a breadth of indications like infliximab, we use it virtually in any of the inflammatory diseases. So, again, we have this great mass of patients on adalimumab. So, unless we can get huge concessions on the biosimilar side, we are going to be in the same hole. So, the bad news is we did not think far enough ahead – well, we could not, you have to contract for now because you have to get the best pricing, and then the problem is you get yourself locked into these dilemmas, which will take some time to unwind.

Over on the pharmacy side, yes, we could implement multiple tiers, and that could even drive existing patients to request going to a biosimilar because it would cost them less out of pocket. However, the wild card there is that manufacturers have very lucrative patient co-payment assistance for non-Medicare patients, and they can afford that by just making up the difference in the payments. So, it is going to be a bit of a back-and-forth for quite a while I think."

US payer

"I have never been a fan of grandfathering, so we will not grandfather. We will either go all-in with the biosimilar or not, otherwise you do not save any money. It has to be [a total switch], because if we say OK, we are going to cover Humira, but we are going to put it in the specialty tier with a co-pay, you can get that for $50, all AbbVie does is give somebody a coupon and it buys down their co-pay of $50, and then why would anybody switch? You know, unless they are sensitive to the cost, but most of these drugs at the prices they are at will chew up the deductible pretty quickly anyway. So, if you want to stay with the brand, sure, maybe you use up your deductible after two months, and with the biosimilar it takes you three months, but you are still going to use it up anyway, so why not use it up fast, and not worry about it?"

US payer

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JAPAN

In Japan, successful pricing outcomes hinge on the product receiving a price premium which can be awarded for added benefit over comparators or for innovation. Pricing and reimbursement decisions are made by the Central Social Insurance Medical Council (Chuikyo) within the Ministry of Health, Labour and Welfare. Pricing and reimbursement processes are closely connected, and the majority of medicines are reimbursed, contingent on the successful outcome of pricing negotiations. The medicine is then listed on the National Health Insurance reimbursement list and can be used in the country.

For newly launched medicines there are two pricing options. Medicines that are novel and for which there are no similar drugs are priced using a cost-based method where drug development and manufacturing, importation, sales and administrative costs, and profits are taken into account. For medicines that show innovation, the allowed operating profit can be increased by 50–100%, compared to the average operating profit of 18.3% in 2013 (Simon-Kucher, 2014). The price is then adjusted if a significant discrepancy exists between the calculated price and the drug's foreign price.

With medicines for which there are similar drugs available in Japan, the cost of the daily dose of the comparator is used to establish a base price (similar efficacy pricing method), to which further premiums are added depending on the additional benefit that the new drug offers compared to the similar drug (see the table below). The price is further adjusted following comparison with foreign prices for the same drug, or, if this is not available, for the comparator drug.

In addition, medicines that are awarded innovation or utility premiums and that are approved in Japan before any other market are granted an additional 10% premium (Simon-Kucher, 2014).

Table 14: **Japan – pricing premiums given to medicines that can demonstrate benefit over comparators**

Type of premium	Premium (%)
Novelty premium	70–120
Utility premium (I)	35–60
Utility premium (II)	5–30
Marketability premium (I)	10–20
Marketability premium (II)	5
Pediatric use premium	5–20

Source: JPMA, 2012

PRICING OF LAUNCHED TREATMENTS FOR CROHN'S DISEASE AND ULCERATIVE COLITIS

Table 15: **Pricing of key marketed Crohn's disease and ulcerative colitis drugs in Japan, 2017**

Drug	Class	CD annual treatment cost ($)	UC annual treatment cost ($)
Humira	TNF-alpha MAb	15,615	15,600
Remicade	TNF-alpha MAb	18,705	18,769
Simponi	TNF-alpha MAb	n/a	30,290
Stelara	IL-12/IL-23 inhibitor	44,492	n/a

IL = interleukin; MAb = monoclonal antibody; TNF = tumor necrosis factor

Source: National Health Insurance drug database

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BIOSIMILAR TNF-ALPHA INHIBITORS IN THE FIVE MAJOR EU MARKETS

INSIGHTS AND STRATEGIC RECOMMENDATIONS

- The European Medicines Agency (EMA) does not make determinations for the substitutability of biosimilars, leaving decisions to national regulators. This has resulted in varied uptake rates for biosimilars across the five major EU markets (France, Germany, Italy, Spain, and the UK), with biosimilar use largely driven by incentives implemented at regional levels.

- Most physicians and payers agree that biosimilars are interchangeable, but introducing biosimilars in new patients and patients unstable on tumor necrosis factor (TNF)-alpha inhibitors is easier than switching patients who are already stable on these therapies. Some physicians are still concerned by treatment continuity and unresponsiveness when switching stable patients, but positive experiences of switching to biosimilar infliximab and promising results from interchangeability studies continue to mitigate these concerns. Payers want the assurance that switching stable patients to biosimilars will generate cost savings.

- Payers agree that a 30% discount is sufficient to implement pro-biosimilar measures, but some are waiting for brand manufacturer response to discounted biosimilar pricing, asserting that there is little incentive to promote biosimilar uptake if the discounts are matched. Other payers contend, however, that they are willing to take on smaller biosimilar discounts or even use biosimilars that have no difference in price to the reference product. Payers with this stance emphasize the importance of having a biosimilar market to engender competition and bring down the prices of reference products.

- Payers are split in their opinions on perpetual switching among biosimilars. Those against multiple switches contend that the costs associated with switching to a new biosimilar and of manufacturing biosimilar products will result in marginal discounts that are not attractive enough to facilitate perpetual switching. Other payers cite that biosimilars are heading toward genericization, therefore they hope that pharmacists will be able to substitute branded products with the biosimilar counterpart in the near future to gain additional discounts.

- Biosimilar TNF-alpha inhibitors will impact price benchmarking for future pipeline biologics, especially if the comparator used has an available biosimilar. Pipeline products with demonstrated superior efficacy against TNF-alpha inhibitors pose a threat to biosimilar uptake, as novel agents – if priced on a par with biosimilars – could become the treatments of choice, thereby necessitating deeper biosimilar discounts.

- The launch of biosimilar infliximab has had a minimal impact on biosimilar use in inflammatory bowel disease (IBD), as reference product Remicade's (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) use is confined to a niche market. Payers expect to implement more stringent biosimilar uptake measures regarding the use of biosimilar adalimumab, as they stand to gain more in cost savings.

- Given satisfactory biosimilar pricing, European payers will utilize varying strategies to promote the uptake of biosimilar TNF-alpha inhibitors, including soliciting tenders and entering into discount agreements for preferred products. These steps, combined with incentives, disincentives, or gain-sharing measures, will be used to enforce compliance in physicians prescribing biosimilar TNF-alpha inhibitors.

THE UPTAKE OF BIOSIMILAR TNF-ALPHA INHIBITORS VARIES ACROSS EU MARKETS, AS THE EMA DOES NOT DETERMINE INTERCHANGEABILITY

The EMA approves biosimilar TNF-alpha inhibitors, but leaves decisions on interchangeability to individual member states, which has led to varied and slow uptake. Biosimilars are determined to be bioequivalent to originator compounds by the EMA after passing safety and efficacy testing, but unlike generic products, biosimilars are not identical compounds. The EMA has chosen not to make a determination on interchangeability for biosimilars, and has left this decision to national regulators (EMA, 2011). As there is no common law to unify biosimilar use, uptake is varied at the national level, and often also at the regional and local level.

Most physicians and payers consider biosimilars as interchangeable and an opportunity to reduce costs, despite the absence of EMA guidance

Despite the absence of EMA guidance on interchangeability, most physicians and payers interviewed by Datamonitor Healthcare believe biosimilars to be interchangeable with their originator products. While payers have long advocated for the use of biosimilars as a result of their cost-saving opportunities, physicians have held some reservations. However, greater experience has been changing physicians' perceptions of biosimilars around Europe, with most commenting that biosimilars have similar efficacy and safety data and demonstrated bioequivalence to their originator product. Most concerns regarding extrapolation and interchangeability have been addressed, especially since physicians have had favorable experiences with infliximab. Continuing education and increasing awareness will remain key to challenging any lingering hesitation around anti-TNF-alpha biosimilars. But, overall, payers and physicians seem to be more aligned in their perception of biosimilars as safe products that can reduce the budget impact of expensive branded products, meaning that more patients can be treated, and the resulting cost savings can be used to reinvest in other services or drugs. Datamonitor Healthcare expects that the increasing receptiveness of payers and physicians to biosimilars will aid biosimilar adoption despite the lack of agreed interchangeability at a centralized level.

"It has been absolutely fine. We have had no issues whatsoever with any of it, otherwise we would not be doing [a switch] again. Patients have not noticed any differences. We have not had any reactions. Our persistence data, so in terms of patients staying on therapy, is exactly the same as it was with the brand in the previous year."

UK regional payer

"At present, we have around 30–40% use of biosimilar infliximab in Spain. [...] In my opinion, the physicians are becoming step by step comfortable with biosimilars. In the beginning, they were very skeptical, we did not have any treatments with biosimilars, but in time and step by step the companies provided good information, some colleagues started a biosimilar because of the price difference, the difference was very big with the biosimilar, the treatment cost was around 10,000 [euros] a year, and the brand cost 15,000 [euros] a year.

I suppose if a new one appears, the physicians will be skeptical, but they have the experience of infliximab, and infliximab is a good experience, the patients are doing well – it is just like the brand, and so the perceptions of biosimilars improved. They do not feel 100% comfortable, but they have begun feeling more comfortable. Other important companies launched a biosimilar too, for example Amgen, MSD [Merck Sharp & Dohme], AbbVie, so it became a trend in time, and they have felt step by step more comfortable."

Spanish local payer

PAYERS RESORT TO BIOSIMILAR QUOTAS TO PROMOTE UPTAKE

Quotas for biosimilar TNF-alpha inhibitors are prevalent in the five major EU markets. The structure of quotas differs slightly among payers, with some opting for a general TNF-alpha inhibitor biosimilar quota, others delineating between intravenous (IV) and subcutaneous (SC) treatment, and another group outlining quotas by active ingredients. Payers also note that indication-specific quotas are not necessary at present as the bulk of infliximab use is in gastroenterology indications in which the drug is more effective, thereby creating a natural separation against other indications such as psoriasis or rheumatoid arthritis.

"We have two different quotas. One quota is a minimum biosimilar quota for subcutaneous biosimilars [which applies to both Enbrel and Humira biosimilars] across all indications, and another quota is a minimum biosimilar quota for all IV biosimilars of anti-TNFs, which is only infliximab currently. But, the quota is on that abstract level – the route of administration. [...] There is no hard case-by-case following, and there is no automatic penalty if the physician starts with Stelara, for example. But he is encouraged with some incentives in the efficiency audit framework if he uses more infliximab [biosimilar] than other drugs. It applies across all the indications, but let us say no-one uses an IV anti-TNF on a voluntary basis, so infliximab is used in IBD and Crohn's because it is more effective there, and the patient takes the burden of IV infusion. For the psoriasis or rheumatoid arthritis, they use subcutaneous, and so there is a natural divide between the anti-TNF biosimilars and their indications, but no formal divide."

German sickness funds payer

"The sick funds want to have as many target quotas as they can. That is the hottest issue currently. They want to see it immediately implemented with a high starting quota in every federal state. [...] Every federal state has negotiated and implemented minimum target quotas for uptake. Each biosimilar quota is active ingredient-specific. That is a big difference compared to the generic target quota. The generic target quota goes over all available generics and there is just one quota for all generics."

German physician association payer

"My hospital belongs to a big organization. It is governmental – the most important organization in Catalonia is the Institut Catala de la Salut, and this organization makes recommendations to incentivize or to have a premium if the prescribers prescribe a percentage of biosimilar. The minimum now is 30% of the total, of the overall prescription of infliximab, but we have a higher bench percentage because we have a lot of patients that begin treatment with the infliximab. Now we have around 40% or 50% of patients treated with biosimilars."

Spanish regional payer

HIGH QUOTAS REQUIRING BIOSIMILAR USE PROMPT MANY PHYSICIANS TO SWITCH PATIENTS

Payers report that encouraging switching has generally not required a separate quota for new patients, and they have rather opted to increase the biosimilar usage quota in general, which has prompted switching in order for physicians to meet these new regulations. Some payers instated smaller quotas in the beginning, before gradually raising the bar, while others took a more aggressive approach. Where quotas are lower, physicians will attempt to prioritize biosimilar use to new patients first, but when quotas are unreachable with new patients alone, they will undertake switching.

"Some federal states have set a very high quota, with less acceptance by the physicians and these huge discussions [regarding whether] to change the patients or not, so we had a federal state which had a 40% minimum quota in the year before Enbrel came to the market, so every physician was aware he could never achieve this quota without switching stable patients, and other federal states did it step by step, [...] it depends upon the federal state.

In my federal state, we do a step-by-step pathway, I think it is part of this 20%, which is very easy to achieve only with initiating new patients, because it is not only completely naïve [patients], it is also patients in anti-TNF cycling. Every time you have a reason to switch with either patients that are naïve or cycling patients, we have measured this proportion and it was about 30% a year switching for any reason, and so we set the quota at 20%, which should be easy to be achieved."

German sickness funds payer

"We never take this into account. We do not care how they reach it. We just implement a quota [...] whether for the new incident cases or for the prevalent cases, we do not care. [The numbers are] just negotiated. It focuses on savings and not on the question of whether we need to

change or switch."

German physician association payer

"If we have problems to achieve this amount, we will consider switching in gastroenterology patients. We have had the experience of switching all the dermatological patients that were treated with infliximab, and we changed all the patients and nothing happened; the patients maintained their response and we do not have additional side effects."

Spanish regional payer

SWITCHING COSTS HAVE LED TO RESERVATIONS AMONG SOME PAYERS, MEANING SWITCHING AMONG MULTIPLE BIOSIMILARS IS UNLIKELY

While payers expect to switch patients to biosimilars given good discounts, some contend that perpetually switching patients from one biosimilar product to the next is not likely. Recognizing that biosimilars are not the same as generics, some payers highlight that each subsequent switch to a new product will therefore require additional investment of time and resources. Additionally, the cost associated with manufacturing biosimilars is high, and payers expect that maximum discounts will be reached quickly, providing little incentive to invest in yet another switch. This group of payers expects that the maximum number of biosimilar products that can be supported in any market will be much lower than observed with generics, with estimates of around three to four products. Despite this, some payers have reported that substantial discounts have prompted them to make switches among biosimilars. Datamonitor Healthcare anticipates that such switching will be exceptional, and that most payers will stick to keeping their preferred biosimilar as it will become more challenging to offer more attractive discounts compared with previous offers.

"We had already switched all our infliximab patients; we are just about to switch them again to make further savings. So, we went to Inflectra or Remsima, we are now going to Flixabi [...] The company wants to get some more data so they have offered us a very good price. So, the discount for us will be significant for moving from one to another. If the discount was between 5% and 10% difference it just probably would not be worth the hassle in terms of switching patients because as I say, we do have to have those conversations with patients. They are not generics and there will be work involved. It is because of that price differential that we are switching again, and I think with a market that is becoming very competitive, we may see bigger differences than I thought maybe a year ago between biosimilar products. Because otherwise they will not get used. Yes, it is huge [the discounts]. So, no, it is because the company wants the data from us, so it is like looking at a clinical trial effectively, so I think our situation will just be local. It is not something that would be replicated nationally."

UK regional payer

"*The discounts just might not be there for the third and fourth time. [...] If a company comes in with a very good price at a tender, then we will be using that for all patients going forward and we will switch them, because also you have to be careful with the tendering because you do not want to award a tender and then not get the volume of patients on to that drug because then actually there is no value in terms of a tendering price, and companies will not offer good prices through tendering. [If] a fourth product gave a very good price at the tendering, there would be an onus on the trust to use that product to maintain the volumes, so it may mean switching patients."*

UK regional payer

However, other payers predict genericization of the biosimilar market, and believe perpetual switching could be more common in the future

While some payers believe that intrinsic limitations in biosimilar manufacturing will preclude biosimilars from being switched

continuously, others think it is only a matter of time before biosimilars are viewed like generics. In places like Spain, switching among biosimilars is already permissible, and payers are pushing for the lowest-cost compound to be purchased. UK physicians, on the other hand, prescribe by brand name, making switching more difficult. Nevertheless, some UK payers believe that the barrier to switching among biosimilars is lower than it was for converting patients from branded products to biosimilar products. Even a practice like perpetual switching could be made attractive as long as stakeholders share savings downstream.

"So, what is interesting is, I think that the resistance is the first step: going from brand to biosimilar. All that resistance was clinician-led. This is my brand. This is my brand. Once they use a biosimilar they have no loyalty. When we start moving around between biosimilars, we are not seeing anyone coming in the way. The resistance was all from parent to biosimilar, not from biosimilar to another one."

UK local payer

"Yes, in some regions like in Andalucía, the infliximab category is used interchangeably, you can only buy the cheapest drug, you have to forget whether it is the originator or the biosimilar, you only buy the cheapest drug. The physician prescribes infliximab, and the pharmacy dispenses the cheaper one only."

Spanish local payer

"Currently it is just the list price competition, and on top of that we have a few of these so-called open house contracts [at the level of the sickness fund], so a minimum additional rebate of, let us say, 10%, and every biosimilar manufacturer that offers that additional rebate gets this contract with the rebate, but it is only a recommendation to the physicians to prefer a rebated biosimilar over an unrebated [one]. There is no hard penalty if they use an unrebated biosimilar, because the quota is the thing which counts, and the other things are softer instruments to further encourage the physician to use a distinct biosimilar, but I think the next step would be making pharmacist switching obligatory for a biosimilar or small molecules, and in this case having a rebate contract or not might be really critical for a manufacturer. At the moment this is not the case, and I do foresee that in the next five years. It is a bit more up to the manufacturer if he believes that it is worth offering the physician an additional 10% to get a preferred recommendation without really [any] consequences."

German sickness funds payer

DISCOUNTS ARE NOT THE ONLY STRATEGY TO FACILITATE SWITCHING AMONG BIOSIMILARS

While discounts are the simplest way to entice payers to switch among biosimilar products, the strategy will inevitably reach an endpoint, and stands to erode the price of biosimilars quickly. Payers assert that alternative strategies, such as reducing wastage through dose banding, are effective, and they are willing to forego minor discounts to attain larger cost savings through more efficient practices.

"*I have seen a bit of both because some of the biosimilars now are playing some interesting value-added service games. So, for example, where we are, we have gone for a more expensive biosimilar because that company are giving us infusion bags ready-made, fixed dose, banded dose, and delivery three times a week, which we love. [As opposed to the competition, which was] just another 10% cheaper. This brings another incentive. [...] This dose banding is also getting incentives, payments. So, if you opt to use dose banding with biosimilars and biologics, we are getting another quarter of a million plus. So, we are now doing that instead, as well."*

UK local payer

TNF-alpha inhibitor biosimilars shift branded products to later lines

Biosimilar infliximab and potentially biosimilar adalimumab will impact not only their reference brands, but will also reduce the sales

potential of other biologics used in IBD by shifting branded products to later lines. Infliximab's use in IBD is more pronounced compared to other inflammatory indications, and therefore payers are more likely to prioritize the drug together with biosimilar adalimumab, pushing interleukins and non-TNF-alpha inhibitors even further down the treatment pathway.

"It will push them further down, no doubt about it. The more and more that we have biosimilar, all that happens is we fill up our sequential treatment basket. It means that the branded products all end up fighting for a very, very compacted space, and most payers will say: 'OK, first line methotrexate, azathioprine, steroid; second line maybe generic Remicade; and third line generic adalimumab, then after that you do IFR Panel [Individual Funding Requests Panel],' for example. So, although officially when NICE approves something we have to have it on the formulary for reimbursement, also in the NICE guidelines it says use the cheapest option in the multi-technology appraisal. So, we do not have to use all of them. We just have to make sure we use NICE-approved ones, and depending on local pricing initiatives they will aim for those ones. You make them aware of it, that is right, and what we tend to do is, if there are certain physicians who are always maybe choosing the more expensive one, then we might go and ask them why they are not looking at the most cost-effective option."

UK local payer

PAYERS USE TENDERS, PHYSICIAN INCENTIVES, AND FORMULARY EXCLUSIONS TO DRIVE BIOSIMILAR UPTAKE

European payers are utilizing various strategies to promote the uptake of biosimilar TNF-alpha inhibitors. These include soliciting tenders and entering into discount agreements for preferred products, or following national guidelines on prescribing to promote uptake. These steps, combined with physician incentives such as gain sharing or penalties linked to target quotas for biosimilar prescribing, are used to drive the uptake of biosimilars. Payers also monitor physician adherence to prescribing the most cost-effective product. While most payers report strategies to increase biosimilar uptake, Italian payers report more relaxed strategies, and do not actively implement any policy to increase biosimilar use. Datamonitor Healthcare expects strategies to evolve in the future, and to shift from offering financial incentives towards favoring penalties or at least disincentives amid changing conditions in the biosimilar landscape.

"So, the government had brought out two or three key documents last year and this year, from April 2017, there is a big financial incentive on biosimilar uptake; a national CQUIN [Commissioning for Quality and Innovation] program. So, this is the first time the government have given a program whereby we are now targeted and we can get significant funds – this is hospital funds – by having targeted switch programs for current and new patients in the biosimilar biologic marketplace. What they have done [via CQUIN] is they have set your one-, two-, and three-year target plans with milestones, and for new patients they have been set at something in the region of 80% and then 90% using the biosimilar. And for current patients, these milestone targets are 50%, then I think 65%, and then 75%. Each hospital can get a minimum of a quarter of a million euros plus for achieving these milestones year on year. This has never been available to use before, and now is driving the biosimilar switch."

UK local payer

"Certainly, in the last two months, from the commissioning perspective, we feel like we have got a lot more sticks that we are prepared to use. [...] We are getting tougher about what we are demanding, whereas before we were not."

UK regional payer

"There is a bonus at the end of the year. The Institut Catala de la Salut makes recommendations, and the director of the hospital makes these recommendations with an objective to achieve at the end of the year. If we achieve it, we receive extra money. It is general because the prescribers have a minimum percentage of prescription of biosimilars, and if this goal is achieved they receive extra money.

They do not have a penalty, but they do not earn this extra money, and we have some difficulties to achieve the minimum that the payer pays per patient and per month if we do not use biosimilars. If the cost is higher, then we over pass this amount."

Spanish regional payer

"The incentive is no penalty by reaching the quota and less bureaucracy, because an efficiency audit is always a lot of work for the physicians. They have to recapitulate the prescriptions of the last two years and to write down reasons for this prescription or that prescription, and if he can avoid that we guarantee him if he reaches his quota there will be no questions for efficient use of anti-TNFs, and so he has a guarantee of not getting bureaucratic overkill. If he misses his quota there is a risk of being penalized; not if he misses the quota for the first time, but if he continuously misses the quota there might be – he has to pay money back, but this is also different between the federal states.

The quotas are made on a federal state basis in Germany, so we have 17 different quotas. The best federal state is currently at nearly 60% Enbrel biosimilar. The weakest federal state is maybe at 10%, and the normal quota, the average across the country, I think is somewhere around 30% minimum biosimilar quota. Some states are still above that quota, and some states are still below, and this quota will rise if adalimumab biosimilars are available. These quotas are renegotiated once a year."

German sickness funds payer

"The quotas work on one side, so they threaten doctors. [...] Every doctor gets audited, and we look at whether they fulfilled the minimum target quota or not. If not, then we go and get details, and the sick funds can calculate the financial damage, as we call it. So, they calculate the actual biosimilar rate of the individual doctor and they compare it with the target quota. They calculate the difference, they multiply it by the number of patients in euros, and then they say: 'OK, you have to pay let us say 80,000 or 100,000 euros penalty.' So, the basic principle here is deterrent.

The treatment-specific financial incentives work completely independently. So, just in theory, one doctor could have to pay a financial penalty and at the same time get the financial incentive.

So, in my case, there was not just one but three sick funds who independently offered me a contract that provides usually 300 to 400 euros per patient to doctors who switch and maintain patients on a [particular brand of infliximab] biosimilar [...] where you have a rebate contract."

German physician association payer

"Certainly when I speak to my clinicians they feel a willingness to switch for a smaller discount, as long as they are getting a percentage of that smaller discount and can put it towards some service development. [...] The money we have saved on the biosimilar switches, part of that has been re-invested and funded more nurse time and more clinic time and more dietician time. [...] So yes, it is about sort of how much are they going to get out of it? They are not just going to do it, because it is workload impact for communication with patients and training patients and that type of thing, particularly if you have got to bring them in for a hospital appointment that you would not be bringing them in for otherwise. Yes, it has got to cover the cost in terms of resource to actually implement it, because none of these are free."

UK regional payer

"AIFA considers biosimilars as different products compared to their originators, not only in the process of registration and pricing, and whatever, but particularly in terms of prescription. [...] The future position of AIFA is not to incentivize, not to promote the use of biosimilars officially, because of course AIFA says biosimilars are good products with a lower price, but you are not forced to prescribe biosimilars. This is in the ability of the prescriber to choose whether he wants to prescribe a biosimilar or the originator, and you know there was a big fight between AIFA and the regions, particularly central and southern Italian regions, which were trying many times to impose the prescription of biosimilars, but they failed every time because the rule is that a doctor is free to prescribe whatever he likes, because biosimilars are not the same molecule, and in fact in many regions where tendering is used, the tenders are not including the same molecule if there are biosimilars and originators. [...] The region asks me every time to check which clinician is prescribing originators instead of biosimilars. [...] These clinicians

who prescribe more originators than biosimilars are eventually asked to explain why, but there is no rule, I mean there is officially no limitation, there is a concern but there is no limitation."

Former Italian national payer

Table 16: **Market access tools used to promote biosimilar TNF-alpha inhibitor uptake in the five major EU markets, by country**

Level	France	Germany	Italy	Spain	UK
National	TC has assessed biosimilar TNF-alpha inhibitors Benepali, Remsima, Inflectra, and Flixabi. All drugs reimbursable in the same population as reference brand	Biosimilars are not substitutable to branded reference product, per the "aut-idem" exclusion list	AIFA does not consider biosimilars to be substitutable	Biosimilars are not considered to be substitutable	NICE assesses biosimilars in a multiple TA with the reference product. No RA biosimilars assessed to date
Regional and local	n/a	All regions have implemented biosimilar quotas in varying forms, as agreed by physicians' associations and sickness funds. Payers use a combination of incentives, disincentives, and gain-sharing agreements to ensure quotas are met	Regional formularies are listed by active ingredients; brand inclusion is not specified. Regional and local tenders conducted for biosimilars may lead to preference of use	None expected at regional level. Local level will contract for best-priced drug (biosimilar or brand)	Biosimilar to become preferred to branded biologics dictated in regional formularies. Step therapy and pathways used to dictate access to branded drugs
Physician	Physicians use brand name prescribing for biologics	Physicians are obliged to meet biosimilar quotas, and may be incentivized to exceed quotas. Some physicians report quotas are minimal and can usually be addressed without switching patients, others report higher quotas are met due to greater incentivization	Choice to treat a patient with a biosimilar is up to the clinician, although step therapy is likely. Clinicians may also need to follow regional regulations, such as biosimilar quotas in regions that have contracts	Physicians are encouraged to use contracted products; no incentive or disincentive specified	Physicians must follow regional or local formularies, and are encouraged to prescribe by brand name. Gain-sharing incentives are utilized to drive uptake

Table 16: **Market access tools used to promote biosimilar TNF-alpha inhibitor uptake in the five major EU markets, by country**

Pharmacist	Substitution permitted against reference product for new treatments only when physician has not specified otherwise. Biosimilars may be substitutable when meeting all conditions listed: patient is informed and has given approval to switch, adequate clinical monitoring and traceability records are maintained	Substitution permitted only if products have the same starting material and the same manufacturing processes. Biosimilar Inflectra is substitutable for Remsima. Otherwise, pharmacists may not substitute biosimilars as part of the "aut-idem" exclusion list	Automatic substitution is not permitted	Automatic substitution is not permitted	Automatic substitution is not permitted
Patient	Patient may override biosimilar substitution, with added out-of-pocket fee	n/a	n/a	No co-pays in the public setting	n/a

AIFA = Italian Medicines Agency; NICE = National Institute for Health and Care Excellence; RA = rheumatoid arthritis; TA = technology assessment; TC = Transparency Committee; TNF = tumor necrosis factor

Source: Datamonitor Healthcare; AEMPS, 2017; AIFA, 2016; ANSM, 2016; DeutschesApothekenPortal, 2016; NICE, 2017

PAYERS ARE WILLING TO IMPLEMENT MORE AGGRESSIVE MEASURES TO PROMOTE BIOSIMILAR UPTAKE

Conversations regarding the outlook for biosimilars and future measures to further promote their uptake reveal that payers are willing to take a more aggressive approach. To do so, they would have to work around national regulations which allow physicians the latitude to prescribe many biologics at second line after failure with conventional therapy. Outside of this, payers will exercise measures to ensure cost-effective options are explored first. UK payers envision handing out fixed payments encompassing an average pricing for TNF-alpha inhibitors. Physicians will still be allowed to choose among their preferred brands, but would need to pay the difference as a premium. Otherwise, Datamonitor Healthcare anticipates that more aggressive biosimilar uptake measures are not likely to be implemented in the near future. Instead, payers will try subtler ways, and will likely resort to a more active stance if softer measures prove to be ineffective.

"With NICE, the TAs will always be mandatory. We cannot narrow it further otherwise it makes a mockery of the national decision-making that NICE has, but as I say what we will do is the situation I just described where we have all the NICE options, but we are kind of forcing the clinicians' hand by saying we will have a minimum price. So yes, fine, you can use everything, but we are only going to pay you so much. [...] We would be likely to have a reimbursement price agreed, so we will pay a contract price whatever that is, if the hospital choose to use something that is more expensive that will have to be done at their own cost. They will only reimburse tender price for that particular molecule. So, ie maybe what they are using is 5% or 10% more, the hospital would have to bear that cost if they did not switch or use those. It would ensure that we were always paying the minimum price and that the hospitals have to use as much of that as they could otherwise they would be at a loss, because we will only reimburse at the cheapest price. At the moment that is the conversation we are having [limited to Remicade versus biosimilar infliximab], but we could widen that at some point in the future to say we have an average TNF price, maybe. I do not think we will do that in the next five years, but at the moment we could do, but I think collaboration might be lost overnight."

UK regional payer

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PRICING IN THE FIVE MAJOR EU MARKETS

Table 17: **Pricing of key Crohn's disease drugs in the five major EU markets, by country, 2017**

Drug	Class	Annual treatment cost ($)				
		France	Germany	Italy	Spain	UK
Entyvio	MAb against alpha-4-beta-7 integrin receptor	15,120	17,199	14,647	25,334	15,801
Humira	TNF-alpha MAb	10,870	21,379	13,870	14,795	10,853
Remicade	TNF-alpha MAb	10,628	20,326	13,891	14,467	12,124
Stelara	IL-12/IL-23 inhibitor	31,121	49,303	34,605	33,565	28,007

Note: Prices listed are ex-manufacturer prices calculated from formulary listings. To view ex-manufacturer price calculations please see the Methodology chapter.

IL = interleukin; MAb = monoclonal antibody; TNF = tumor necrosis factor

Source: British National Formulary, 2016; Catalogo de Medicamentos, 2016; L'Informatore Farmaceutico, 2016; Le Dictionnaire Vidal, 2016; Rote Liste, 2016

Table 18: **Pricing of key ulcerative colitis drugs in the five major EU markets, by country, 2017**

Drug	Class	Annual treatment cost (£)				
		France	Germany	Italy	Spain	UK
Entyvio	MAb against alpha-4-beta-7 integrin receptor	15,210	17,160	14,625	25,350	15,795
Humira	TNF-alpha MAb	10,920	21,424	13,832	14,768	10,816
Remicade	TNF-alpha MAb	10,725	20,231	13,894	14,625	12,188
Simponi	TNF-alpha MAb	24,830	44,460	30,030	32,110	23,530

Note: prices listed are ex-manufacturer prices calculated from formulary listings. To view ex-manufacturer price calculations please see the Methodology chapter.

Source: British National Formulary, 2016; Catalogo de Medicamentos, 2016; L'Informatore Farmaceutico, 2016; Le Dictionnaire Vidal, 2016; Rote Liste, 2016

FRANCE

INSIGHTS AND STRATEGIC RECOMMENDATIONS

- Access conditions for inflammatory bowel disease (IBD) medications in France are determined nationally through Transparency Committee (TC; Commission de la Transparence) guidelines. Without head-to-head trials against tumor necrosis factor (TNF)-alpha inhibitor Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe), later entrants have had a challenging time attaining added benefit. Entyvio (vedolizumab; Takeda) and Humira (adalimumab; AbbVie/Eisai) received no added benefit in any of the populations tested for ulcerative colitis (UC), while Humira (adalimumab; AbbVie/Eisai) and Simponi (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) also had the same evaluation in Crohn's disease (CD). Remicade, the first entrant in both UC and CD, is the only IBD drug to have earned a major added benefit rating in pediatric UC and CD, as well as in adult UC. Remicade also has a moderate benefit in patients with moderate to severe CD.

- For CD, both Stelara (ustekinumab; Johnson & Johnson/Mitsubishi Tanabe) and Entyvio are restricted to patients who are contraindicated or intolerant to, or who have failed TNF-alpha inhibitor therapy, as neither of the compounds has head-to-head trials. Despite this, Stelara is advantaged over Entyvio in active CD, as the IL-12/23 has a minor added benefit, while Entyvio failed to attain any added benefit and only achieved a moderate medical benefit rating. Entyvio's weaker efficacy results have left a clear road for Stelara to gain market share in TNF inhibitor-failure patients.

- For UC, Entyvio is restricted to patients who are contraindicated or intolerant to, or who have failed TNF-alpha inhibitor therapy, but the drug fares better in this indication with a minor added benefit due to a stronger demonstrated clinical benefit versus placebo in inducing clinical response and maintaining clinical remission.

- A mixed added benefit in CD and UC means Entyvio is added to the "liste en sus" only for use in UC, while it failed to get on the list for CD. Although the lack of listing in CD does present an access hurdle, high co-morbidity between CD and UC means patients could receive Entyvio when symptoms of both diseases are present. Entyvio is not likely to be added to the list for use in CD unless payers are presented with new evidence.

- Added benefit for etrolizumab (Roche) hinges on the absolute improvement the drug demonstrates in Phase III trials. Payers do not think achieving an additional medical benefit (ASMR; amélioration du service médical rendu) rating of III or IV is likely in first-line settings, as the drug will need to show absolute improvement over comparators infliximab and adalimumab during the induction and maintenance phase, and to do so with well-powered clinical trial data. Payers say that a better strategy is to price etrolizumab comparably with biosimilar infliximab, since there is strong pricing pressure for manufacturers to reduce price in this patient population.

- Etrolizumab's subcutaneous (SC) formulation will provide the drug with an advantage over Entyvio's intravenous (IV) formulation, as this means the former does not need to qualify for liste-en-sus status. However, both are unlikely to be favored ahead of infliximab due to the TNF inhibitor's high level of familiarity among gastroenterologists.

ASMR RATING HAS AN IMPACT ON PRICING

In France, the TC within the French National Authority for Health (HAS; Haute Autorité de Santé) evaluates all new medicines for medical benefit and added benefit over appropriate comparators, and assigns one or more ASMR ratings (see the table below). The

TC's evaluations serve as a basis for pricing negotiations between the manufacturer and the Economic Committee on Healthcare Products, and it also recommends a reimbursement level for the medicine.

Table 19: **Transparency Committee's ASMR ratings and pricing implications**

ASMR rating	Benefit over comparator	Pricing implication
I	Major	Price comparable to Germany, Italy, Spain, and UK prices
II	Important	Price comparable to Germany, Italy, Spain, and UK prices
III	Moderate	Price comparable to Germany, Italy, Spain, and UK prices
IV	Minor	Price similar to or slightly above comparator treatments
V	No benefit	Discount to comparator treatments required
VI	Less effective	Not reimbursed
ASMR = additional medical benefit		

Source: Grandfils, 2008

The TC determines the level of medical benefit, which then impacts on the National Union of Health Insurance Funds' decision on the reimbursement level, as summarized in the table below.

Table 20: **Transparency Committee's SMR ratings and pricing implications**

SMR rating	Benefit over comparator	Reimbursement	
		High disease severity	Low disease severity
I or II	Major or important	100% or 65%	65%
III	Moderate	30%	30%
IV	Weak	15%	15%
V	Insufficient	0%	0%
SMR = medical benefit			

Source: HAS, 2014a

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

Drug	Reimbursement status	Reimbursement lists	TC's reimbursement recommendation	Patient population	Line of therapy	SMR	ASMR	Comparator	Notes	Date

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

Entyvio	Reimbursed (hospital: 100%)	C, T	Reimbursed	Patients with moderate to severe active CD with failure (inadequate response, loss of response, or intolerance) on CSs, immunosuppressants, and anti-TNF agents	Third	Moderate	V (none)	None; TNF-alpha inhibitors used clinically	There are no head-to-head trials available for Entyvio against long-term TNF-alpha inhibitor use. Results in TNF-alpha inhibitor-naïve patients demonstrated modest clinical benefit for co-primary endpoint of induction of clinical remission against placebo at six weeks, and failed second co-primary endpoint of CDAI >100 at six weeks. Entyvio failed the trial's	January 2015

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

									primary endpoint in patients refractory to TNF-alpha inhibitors. Entyvio has an RMP, and prescription is through gastroenterologists. There are ongoing head-to-head trials of Entyvio with other biologics. The final report is due in June 2022	

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

Entyvio	n/a	n/a	n/a	Patients with moderate to active CD who are naïve to TNF-alpha inhibitor therapy	Second	Insufficient	n/a	n/a	There are no head-to-head trials available for Entyvio against TNF-alpha inhibitors. This patient population is outside of the ATU granted for the drug	January 2015

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

Humira	Reimbursed (ambulatory: 65%; hospital: 100%)	A, C, T	Reimbursed (65%)	Adults with moderate active CD and are who are intolerant, contraindicated, or inadequate responders to a full and adequate course with a CS and/or an immunosuppressant	Second	Important	V (none)	Remicade	There are no head-to-head data for Humira against Remicade. The TC does not expect Humira to provide additional benefit in mortality or morbidity. However, Humira could reduce impact on the healthcare system and improve QoL owing to its SC method of administration. This benefit is, however, only theoretical	July 2013

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

Humira	Reimbursed (ambulatory: 65%; hospital: 100%)	A, C, T	Reimbursed (65%)	Children (at least six years old) with severe acute CD who have not responded, intolerant, or contraindicated to conventional treatment (CSs, immunomodulators, or first-line nutritional treatment)	Second	Important	V (none)	Remicade	There are no clinical data for Humira against Remicade. The TC does not expect Humira to provide additional benefit in mortality or morbidity. However, Humira could reduce impact on the healthcare system and improve QoL owing to its SC method of administration. This benefit is, however, only theoretical.	July 2013

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

Humira	Reimbursed (ambulatory: 65%; hospital: 100%)	A, C, T	Reimbursed (65%)	Severe active CD patients who are intolerant, contraindicated, or have not responded to a full and adequate course of therapy with a CS and/or an immunosuppressant. CS combination therapy is required for induction treatment unless intolerant or contraindicated	Second	Important	V (none)	Remicade	There are no clinical data for Humira against Remicade. The TC does not expect Humira to provide additional benefit in mortality or morbidity. However, Humira could reduce impact on the healthcare system and improve QoL owing to its SC method of administration. Specialist opinion also believes the size of the effect of Humira and Remicade is	October 2007

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

									comparable in induction and maintenance. Initial prescription at hospitals is restricted to gastroenterology specialists	

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

Remicade	Reimbursed (hospital: 100%)	C, T	Reimbursed (n/a)	Adults with moderate active CD and who are intolerant, contraindicated, or inadequate responders to a full and adequate course with a CS and/or an immunosuppressant	Second	Important	III (moderate) (2004)	None	At the time of evaluation, Remicade was the only drug available for moderate active CD. Given data from one clinical study, the TC expects Remicade will have a moderate impact on morbidity (CS-free clinical remission) and QoL. Additional QoL improvements with AZA via IBDQ are not clinically relevant. Data also do not support early treatment resulting in	October 2012

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

									fewer hospital admissions or in a delay in the need for abdominal surgery	

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

Remicade	Reimbursed (hospital: 100%)	C, T	Reimbursed (n/a)	Children (6–17 years of age) with severe active CD, who are intolerant, contraindicated, or have not responded to conventional treatment (CS, immunosuppressant, and nutritional treatment). Study is conducted only in combination therapy with immunosuppressants	Second	Important	II (important)	None	At the time of evaluation, Remicade was the only drug available for pediatric CD. Even though the available data do not provide information on Remicade's effect on mortality or surgery, the lack of available alternatives gives reason that Remicade may contribute to reducing morbidity and mortality, specifically on linear growth and weight gain	March 2009

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

Remicade	Reimbursed (hospital: 100%)	C, T	Reimbursed (n/a)	Patients with severe or fistulizing active CD who are either contraindicated, intolerant, or refractory to conventional treatment	Second	Important	III (moderate)	None	There was no alternative medication for this patient population at the time of evaluation. Remicade every eight weeks demonstrated an 18% greater proportion of patients in clinical remission at week 20 and a longer median time to relapse (19 weeks). Patients with fistulizing active CD also experienced an increase in median time to relapse (26	September 2004

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

									weeks). Additionally, 48% of patients with severe active CD had responded by week 12	

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

Stelara	Reimbursed (ambulatory: 65%; hospital: 100%)	A, C, T	Reimbursed (65%)	Patients with moderate to severe active CD with failure (inadequate response, loss of response, or intolerance) on CSs, immunosuppressants, and anti-TNF agents	Third	Important	IV (minor)	TNF-alpha inhibitors	Stelara is predicted to impact morbidity in trials with TNF-alpha inhibitor-refractory and -naïve patients (UNITI I and UNITI II). Stelara met primary and secondary endpoints against placebo during the induction phase of both trials. Stelara also met the primary endpoint in the maintenance phase against placebo, but failed to	March 2017

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

									demonstrate significant differences in various secondary endpoints. Stelara was given ATU status in November 2015 for adults with moderate to severe active CD, in adults who have failed Remicade, Humira, or Entyvio, or who are intolerant or contraindicated. The ATU is enforced until conditions for the 130mg bottle have been	

Table 21: **Transparency Commission's assessment of Crohn's disease treatments**

									developed	
Stelara	n/a	n/a	n/a	Patients with moderate to active CD who are naïve to TNF-alpha inhibitor therapy	Second	Insufficient	n/a	n/a	There are no head-to-head trials available for Stelara against TNF-alpha inhibitors. This patient population is outside of the ATU granted for the drug	March 2017

Note: Reimbursement lists: A = assuré sociaux (ambulatory drugs – oral and self-administered drugs); C = collectivité (drugs used in hospitals included in the DRG reimbursement); T = inclusion on "liste en sus"

ASMR = additional medical benefit; ATU = temporary authorization for use; AZA = azathioprine; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CS = corticosteroid; DRG = Diagnosis-Related Groups; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; QoL = quality of life; RMP = risk management plan; SC = subcutaneous; SMR = medical benefit; TC = Transparency Committee; TNF = tumor necrosis factor

Source: HAS, 2004; 2007b; 2009; 2012b; 2013b/c; 2017

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

Drug	Reimbursement status	Reimbursement lists	TC's reimbursement recommendation	Patient population	Line of therapy	SMR	ASMR	Comparator	Notes	Date

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

Entyvio	Reimbursed (hospital: 100%)	C, T	Reimbursed (n/a %)	Patients with moderate to severe active UC with failure (inadequate response, loss of response, or intolerance) on CSs, immunosuppressants, and anti-TNF agents	Third	Important	IV (minor)	None; TNF-alpha inhibitors used clinically	Results of the GEMINI I study in patients with prior failure on CSs, immunomodulators, or Remicade demonstrated moderate impact on morbidity based on superior results in clinical remission at week 52 over placebo and a statistically and clinically relevant improvement in QoL (mean improvement from baseline IBDQ) at week 52. Entyvio was granted	January 2015

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

									ATU status until September 2014 for patients with prior therapeutic failure to TNF-alpha inhibitors. Entyvio has an RMP, and prescription is through gastroenterologists. There are ongoing head-to-head trials of Entyvio with other biologics. The final report is due in June 2022	

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

Entyvio	n/a	n/a	n/a	Patients with moderate to severe active UC who are naïve to TNF-alpha inhibitor therapy	Second	Insufficient	n/a	n/a	There are no head-to-head trials available for Entyvio against TNF-alpha inhibitors. Systematic review and network meta-analysis was performed based on available data, which included eight randomized and 10 double-blinded controlled studies comparing Humira, Simponi, Remicade, and Entyvio. Results demonstrated	January 2015

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

									efficacy of biologics compared to placebo, but as there were only a limited number of studies and no head-to- head comparison, there is a high risk of bias in the assessment. The committee found the studies to be unethical as placebo was used as a comparator when other drugs were available to treat the disease, and asserted the need for direct	

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

									comparison studies. Additionally, this patient population is outside of the ATU granted for the drug	

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

Humira	Reimbursed (ambulatory: 65%; hospital: 100%)	A, C, T	Reimbursed (65%)	Adults with moderate to severe active hemorrhagic UC who are intolerant, contraindicated, or have not adequately responded to conventional treatment (CS, 6-MP, or AZA)	Second	Important	V (none)	Remicade	There are no head-to-head trials of TNF-alpha inhibitors to ascertain therapeutic placement. Humira has a low impact on morbidity and QoL compared to placebo (10% more patients on Humira improved at least 16 points in IBDQ score at week 52). Humira is superior on the primary endpoint of the proportion of patients naïve to TNF-alpha inhibitors in	October 2012

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

									clinical remission at week 8, but the difference was modest (9.3%), and the 80/40mg dosing used is not authorized per the marketing authorization (ULTRA-1). In ULTRA-2, a greater proportion of patients on Humira were in clinical remission at week 8, but this was true only for TNF-alpha inhibitor-naïve patients, and not for patients refractory to	

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

									TNF-alpha inhibitors. Additionally, the percentage of patients in clinical remission at week 52 was lower in patients who had not achieved early remission (week 2 or week 8). Following this, the SPC was amended to discontinue treatment in patients who have not responded in weeks 2 to 8. Humira is an exception drug, initial prescription is	

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

									reserved for gastroenterologists	

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

Remicade	Reimbursed (hospital: 100%)	C, T	Reimbursed (65%)	Adults with moderate to severe active hemorrhagic UC who are intolerant, contraindicated, or have not adequately responded to conventional treatment (CS, 6-MP, or AZA)	Second	Important	II (important)	Humira and Simponi (ASMR shared)	Re-evaluation did not change assessment rating. Additional data submitted from extension study of two pivotal trials confirm the efficacy of Remicade on morbidity (PGA score) and QoL (IBDQ), but the results of the OPUS registry study only confirm safety data and not long-term efficacy. There also remains poor documentatio	May 2014

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

									n on the impact of Remicade on reducing the need for colectomy. Hospitalization data submitted containing date of first endoscopy to colectomy in patients taking Remicade or chemotherapy remain exploratory. Remicade is a hospital drug. Prescribing should be in line with dosing stated in the marketing authorization	

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

Remicade	Reimbursed (hospital: 100%)	C, T	Reimbursed (n/a)	Children and adolescents (aged 6–17 years) with severe active UC, contraindicated, intolerant, or have had inadequate response to conventional therapy (CS, 6-MP, AZA)	Second	Important	II (important)	CS or surgery (no TNF-alpha inhibitors)	Remicade's ASMR is important due to the disease's rare occurrence, and since severe forms of the disease affect children disproportionately. Results from Study C0168T72 demonstrated reduced clinical symptoms (Mayo score) and a similar level of effect as adult patients with UC. However, the study did not have information on the impact of Remicade on	March 2013

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

									the need for surgery and/or mortality, nor any long-term reduction in use of CSs	

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

Remicade	Reimbursed (hospital: 100%)	C, T	Reimbursed (65%)	Adults with moderate to severe active UC who are intolerant, contraindicated, or have not adequately responded to conventional treatment (CS, 6-MP, or AZA)	Second	Important	II (important)	None	Remicade is superior to placebo in the primary endpoint of the proportion of patients with clinical response at week 8, and for all secondary endpoints: clinical response at week 30, clinical remission, mucosal healing, CS withdrawal, hospital admissions, and QoL. Most patients had moderate cases of UC, very little data were for	July 2007

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

									severe patients. The TC expects Remicade to have an impact on morbidity and QoL. Additionally, there was no alternative drug in this subpopulation during the time of the assessment	

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

Simponi	Reimbursed (ambulatory: 65%; hospital: 100%)	A, C, T	Reimbursed (65%)	Adults with moderate to severe active hemorrhagic UC who are contraindicated, intolerant, or have not responded adequately to a conventional treatment (CS, 6-MP, or AZA)	Second	Important	V (none)	TNF-alpha inhibitors	Without an active comparator trial, it is not possible to place Simponi in the therapeutic pathway. Induction study demonstrated superiority over placebo in the primary endpoint of clinical response at week 6 (PURSUIT). Clinical remission in the induction phase was a secondary endpoint, which was against the recommendati	February 2014

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

									on of the TC, which would have preferred this as a primary endpoint. There is a statistically significant difference favoring Simponi over placebo in secondary endpoints of clinical remission and mucosal healing. Maintenance study demonstrated greater sustained clinical remission at week 54 against placebo.	

Table 22: **Transparency Commission's assessment of ulcerative colitis treatments**

									Simponi is an exception drug, initial prescription is restricted to hospitals by gastroenterologists	

Note: Reimbursement lists: A = assuré sociaux (ambulatory drugs – oral and self-administered drugs); C = collectivité (drugs used in hospitals included in the DRG reimbursement); T = inclusion on "liste en sus"

6-MP = mercaptopurine; ASMR = additional medical benefit; ATU = temporary authorization for use; AZA = azathioprine; CS = corticosteroid; DRG = Diagnosis-Related Groups; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; PGA = physician's global assessment; QoL = quality of life; RMP = risk management plan; SMR = medical benefit; SPC = supplementary protection certificate; TC = Transparency Committee; TNF = tumor necrosis factor; UC = ulcerative colitis

Source: HAS, 2007a; 2012a; 2013a; 2014b/c; 2015

IN THE ABSENCE OF HEAD-TO-HEAD TRIALS VERSUS TNF INHIBITORS, LATER ENTRANTS LARGELY RECEIVE NO ADDED BENEFIT

Since the manufacturers of UC and CD biologics have conducted studies against placebo, the TC has determined that most of the drugs offer no added benefit over comparators. Later entrants Entyvio and Humira received no added benefit in any of the populations tested for UC, while Humira and Simponi received the same evaluation in CD. The absence of head-to-head trials fails to illustrate an appropriate therapeutic pathway, the TC stated, and therefore at best these later entrants could be considered as alternatives, but not the favored biologic of choice.

These decisions demonstrate the critical role that head-to-head trials play in contributing to pricing and reimbursement decisions. Indirect comparisons or strong results against placebo are not enough to earn a higher ASMR rating and give better pricing prospects. Remicade, the first entrant in both UC and CD, is the only IBD drug to have earned a major added benefit rating in pediatric UC and CD, as well as in adult UC. Remicade also has a moderate benefit in patients with moderate to severe CD.

ACCESS TO STELARA AND ENTYVIO IS RESTRICTED TO TNF-FAILURE PATIENTS IN CD AND UC RESPECTIVELY

Stelara and Entyvio are both reimbursed only when a patient has failed or is contraindicated or intolerant to TNF-alpha inhibitors, despite having marketing authorizations for use prior to TNF-alpha inhibitor-failure. The TC asserted that as there were no head-to-head trials against TNF-alpha inhibitors, these new agents could not be added alongside TNF-alpha inhibitors at the second line. Additionally, the TNF-alpha inhibitor-naïve population falls outside of the “temporary authorization for use” (ATU; Autorisation temporaire d'utilisation), giving further credence to excluding this patient population from reimbursement. As Stelara and Entyvio are reserved for third-line use, Datamonitor Healthcare anticipates market uptake for these drugs will be limited.

Stelara received a more favorable added benefit rating than Entyvio in CD

Despite being reserved for third-line use in CD, Stelara has better positioning than its direct competitor, Entyvio. This is because Stelara received a minor added benefit over TNF-alpha inhibitors, while Entyvio received a no added benefit rating and only a moderate SMR rating. The committee cited that a strong evidence package clearly demonstrating absolute benefit in the TNF-alpha inhibitor-refractory population was an important factor in this added benefit for Stelara. Stelara met all of its primary endpoints in patient populations naïve to TNF-alpha inhibitors and for patients refractory to the biologics. Entyvio, on the other hand, met its primary endpoint in patients naïve to TNF-alpha inhibitors, albeit with modest results, but failed to meet its primary endpoint in the refractory patient population.

A single infusion of Stelara 6mg/kg demonstrated a statistically significant improvement over placebo on the primary endpoint of clinical response at six weeks for patients with prior TNF failure and those who are TNF-alpha inhibitor-naïve in the UNITI I and UNITI II trials (ClinicalTrials.gov identifiers: NCT01369329; NCT01369342). Clinical response at week 6 in UNITI I was 34% versus 21% in placebo-treated patients, while clinical response at six weeks for patients in UNITI II was 56% versus 29% in placebo-treated patients. This translated to an absolute difference of 12.3% in UNITI I (95% confidence interval [CI]: 4.5–20.1%) and 26.8% in UNITI II (95% CI: 18–36%).

Stelara also demonstrated a statistically significant improvement on the secondary endpoints of clinical remission and response at week 8, and decrease from baseline in Crohn’s Disease Activity Index (CDAI) score of 70 points or greater at weeks 3 and 6.

Entyvio’s results from GEMINI II in TNF-alpha inhibitor-naïve patients demonstrated modest clinical benefit of questionable relevance.

Entyvio demonstrated a statistically significant difference in the co-primary endpoint of induction of clinical remission against placebo at six weeks, at a modest absolute difference of 7.8% (95% CI: 1.2–14.3%; p=0.02), which was lower than expected per the study protocol (16%). Entyvio also failed to meet a second co-primary endpoint of clinical response (greater than or equal to a 100-point decrease in the CDAI score) at week 6. In the GEMINI III study of patients who had failed on TNF-alpha inhibitor agents, Entyvio also failed to demonstrate a difference against placebo on the primary endpoint of clinical remission at week 6. Due to these weaker trial results, Datamonitor Healthcare anticipates that Entyvio will not be a major threat to Stelara attaining market share among the TNF inhibitor-refractory population.

"At the end of the day, [for Entyvio] in Crohn's disease, it was not just the lack of appropriate design, it was also the effect size. The effect size is so small against placebo that the Transparency Committee's gut feeling was that it is likely to be not non-inferior but slightly inferior to anti-TNF-alpha in Crohn's disease, where because of the unmet need in second line it is difficult to say no, which means that in Crohn's disease it would go clearly on infliximab for first line, or adalimumab, or another anti-TNF-alpha, there are only three registered I think in the EU, and if you fail then you can cycle or you can also go to Stelara in second line, and if you fail again after Stelara then on a named patient basis I think at least in large academic hospitals you may have access with hospital funding only – it is not unthinkable if you are not eligible for a clinical trial to get access to vedolizumab."

Former French national payer

ENTYVIO GETS ADDED BENEFIT IN TNF-ALPHA-REFRACTORY UC PATIENTS

The TC awarded Entyvio a minor added benefit for UC patients with moderate to severe symptoms and failure on corticosteroids, immunosuppressants, and anti-TNF agents. The results of the GEMINI I study in patients with prior failure on corticosteroids, immunomodulators, or Remicade demonstrated a benefit versus placebo in inducing clinical response and maintaining clinical remission. A greater proportion of patients on Entyvio achieved the primary endpoint of clinical response at week 6, and also demonstrated superiority on the secondary endpoints of clinical remission and mucosal healing. Given the lack of alternatives in this patient subgroup, this was considered sufficient to receive a minor added benefit.

Entyvio is added to the liste en sus only in UC, with limited access in CD

As Entyvio only received a moderate level of SMR in CD, it has not been added to the liste en sus used to fund the utilization of expensive therapies in the hospital setting that cannot be funded appropriately through the French DRG system. Since 2015, a drug's SMR and ASMR ratings have had an impact on its likelihood of being added to the liste en sus, with access reserved for drugs that have an SMR rating of "major" or "important." Further, if a drug has no comparators on the liste en sus and has an ASMR of IV or V, it is also generally not added to the list. Entyvio received an SMR rating of "important" in UC, but only "moderate" in CD, resulting in only partial listing. The lack of listing for CD presents a significant access hurdle for the drug. Payers say, however, that as patients often have overlapping CD and UC symptoms, it is feasible that CD patients could receive Entyvio.

French payers interviewed by Datamonitor Healthcare say that Entyvio's status on the liste en sus is unlikely to change in the near future. Entyvio will continue to be excluded from the list for CD, as long as the drug has an SMR of moderate. Payers say that unless there is new evidence to change the SMR to important or major, the status will remain unchanged. There is also no danger of Entyvio being removed from the list for UC as it is currently reimbursed only for TNF-alpha-refractory patients, and for this patient population there is no suitable comparator. Infliximab is the comparator for patients who are naïve to TNF-alpha inhibitors, but Entyvio is not reimbursed for this patient population. Hence, the removal of infliximab from the liste en sus would not trigger the delisting of Entyvio.

"If they come with very well-worded evidence of some new information that is convincing enough to change the SMR given the uptake, or maybe a head-to-head study, then of course it can change. For example, if they do a head-to-head study against infliximab demonstrating

that it would be as good, then of course you can change.

I do not think that even clinicians would push dramatically, the only thing is the definition, where as you may know, some patients have an overlap, they have both Crohn's and ulcerative colitis, it is a minority but of course academics are very concerned about those patients, so I think the sick fund, the regional authority would be quite flexible on the definition of those patients, so that would also be a way to give access, where the clinician would say, 'well, he has Crohn's but he also has ulcerative colitis.'"

Former French national payer

ETROLIZUMAB'S ASMR HINGES ON EFFICACY DATA DEMONSTRATING ABSOLUTE IMPROVEMENT OVER INFLIXIMAB

The level of added benefit that etrolizumab will achieve will depend on the absolute improvement demonstrated in its Phase III trials. French payers state that to achieve an "important" ASMR II, etrolizumab will need to show clear absolute improvement for both induction and sustained remission, and with well-powered clinical trial data. Payers believe that while absolute improvement of around 10% would result in ASMR IV, a difference of around 50% would result in ASMR II.

"*If you have a 10% absolute improvement in achieving remission at week 6 or week 8, and this 10% remains the same at week 52, and it is powered for both, so induction and remission – usually it is two different studies, so it is demonstrated as a primary endpoint but it can be a co-primary endpoint, it is not an issue at all, and if it is well designed and well powered and you have 10% absolute difference, then for sure you would get ASMR IV. If you have let us say 20–30% difference you would get ASMR III, if you have 50% difference you would get ASMR II, and so on and so forth, why not? Because if you look at the baseline it is pretty low for these patients. […] If I have 60–80% of the patients in remission at 52 weeks instead of, maybe, I do not know, 10–20% today, it would be a huge difference, and you would gain an ASMR II. Now, if the absolute difference is just 10%, it is better than nothing, you would get an ASMR IV."*

Former French national payer

Roche will have to present robust data on superiority to infliximab in order to be judged to have an added benefit if it aims to achieve a price for etrolizumab above that of infliximab in the first-line biologic setting. The design of the Phase III trials comparing etrolizumab to infliximab and adalimumab will also be studied carefully by the TC if the manufacturer is aiming to achieve an added benefit assessment.

"The question is, is the study powered to demonstrate maintenance of remission against infliximab at 52 weeks. […] So, maybe they are in a position to demonstrate non-inferiority against infliximab. What is very important is to know whether the [GARDENIA] study was designed to demonstrate superiority or just non-inferiority, and if yes, how they have defined the margins for non-inferiority."

Former French national payer

Interviewed payers do not consider it likely that an ASMR rating of IV or III will be achieved, and instead suggest that in order to achieve access to the first-line biologic setting, pricing comparable with biosimilar infliximab will be necessary, as the Healthcare Products Pricing Committee (CEPS; Comité economique des produits de santé) will be able to exert pricing pressure in this line of therapy.

"The question would be, what is the indirect comparison from HICKORY and LAUREL with vedolizumab, because it is the same mechanism of action. Is it non-inferior? […] So the best you may achieve for this drug would be ASMR V in the second line, and SMR important. [Etrolizumab would get] an ASMR V in the first line, but the first line is massive. So, the question is, what is the price assumption, are they happy with a biosimilar-like price, and to have the full market, and have a very good market penetration in a short period of time, which might be a

strategy for them especially because the list price of infliximab biosimilar is quite high in France again, because of this mechanism. Then you could have what we call a fast track, you can claim reimbursement saying I am as good as vedolizumab in second line, and infliximab in first line, therefore you anchor your price negotiation, so you can be at the price of the biosimilar, so the weighted average price of the two target populations between vedolizumab and infliximab biosimilar with of course a discount in order to gain quick market access. For example, you are almost at parity with the biosimilar price, but you can also treat patients in second line, again a huge market penetration. It is not that your price negotiations are likely to be very long because the economic committee would have an advantage to have many competitors and say in any case we can wait, how many integrin drugs are in the pipeline in second line, how many other drugs with a different mechanism of action such as anti-IL [...] and so on are in the pipeline coming for those indications that can compete on price. If you have huge pressure the economic committee would try and take an advantage."

Former French national payer

Etrolizumab will not need to qualify for liste-en-sus status

Etrolizumab's SC formulation will be an advantage for launching in France over Entyvio's IV formulation, as SC administered drugs do not need to qualify for liste-en-sus status. Although the drug will likely be initiated in hospitals by gastroenterologists, and use will be tied to the hospital budget, patients will be managed by community physicians after the initiation process. Datamonitor Healthcare anticipates that in France, IV versus SC administration will have a greater impact on accessibility, highly favoring SC drugs as hospitals need to ensure that IV administered drugs have liste-en-sus status in order to receive additional payment on top of the DRG payment. Even so, payers do not think that etrolizumab or Entyvio will be favored ahead of infliximab, as physicians are conservative with their prescribing, and infliximab has both long-term efficacy and safety data.

"[Etrolizumab] is still hospital-initiated, so they would have to report in their budget, so there might be a new management tool for those prescriptions initiated by the hospitals, and also usually clinicians love to initiate those drugs within the hospital, in day care or full hospitalization depending on the severity of the condition. So, when they know that the patient has achieved remission, they are likely to switch those patients from the tertiary centers to the community, and to a community gastroenterologist who would renew the drug, and they would see this patient again in 12 months from now. But in the first place, maybe they prefer – for example, the patient is just diagnosed (naïve patient) – you need education of these patients, because they cannot do an injection themselves without proper education, you need to be sure about the compliance of these patients, that they have well understood the pros and the cons, and why they should take their drugs, be aware of side effects, report side effects, and so on and so forth. So, for this reason, most of the time the patient would stay three days at the hospital to have a full diagnosis; you have Crohn's disease, you start the drug, so it would be difficult for them to say we will initiate the treatment after discharge.

[Etrolizumab will not go on the liste en sus,] but it might be a matter of choice where they will say, let us stick with infliximab as we have already done, if the patient is not responding we can switch to this one with the subcutaneous (administration) for example, or if the patient is not willing to go on infliximab then the question would be what is the difference between adalimumab – well in short words, it would be mostly physician preference, with some managing the tools put in by local regional payers that could be a barrier, because it is not like psoriasis, you would never have the patient in the hospital with psoriasis."

Former French national payer

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GERMANY

INSIGHTS AND STRATEGIC RECOMMENDATIONS

- Amid ongoing reforms, physicians' prescribing limits (Richtgroessen) or practice peculiarities (Praxisbesonderheiten), which exempt drugs from prescribing limits, are becoming less relevant, with sickness funds moving towards new types of efficiency audits and contract arrangements with manufacturers. Tumor necrosis factor (TNF)-alpha inhibitors have traditionally faced few access hurdles, having been exempt from prescribing limits, but prescribing quotas will be the main mechanisms limiting access to branded biologics in the future.

- A recent legislative change paves the way for the introduction of a new prescribing system that will notify physicians when a lower-priced alternative exists if they prescribe a drug for a patient population with no added benefit. Once implemented, this tool will mostly impact drugs in which a mixed added benefit has been assessed for some subpopulations and not others. As the process may open physicians up to efficiency audits, it is likely that the ruling will pressure physicians to prescribe drugs where an added benefit has been assessed.

- The Federal Joint Committee (G-BA; Gemeinsamer Bundesausschuss) did not award added benefit to Entyvio (vedolizumab; Takeda) in ulcerative colitis (UC) or Crohn's disease (CD) for patients naïve or refractory to TNF-alpha inhibitors, as there were no head-to-head trials for the drug. The manufacturer did not submit a dossier for CD, and adjusted indirect assessments of Humira (adalimumab; AbbVie/Eisai) and Entyvio against placebo in UC could not be conducted due to differing clinical trial designs. Due to this absence of added benefit, Entyvio's price is in line with other TNF-alpha inhibitors.

- Etrolizumab (Roche) will likely get a mixed benefit assessment by the G-BA, and its price will be dependent on the patient population that receives the added benefit. Payers expect a price between those of the biosimilar TNF-alpha inhibitors and Stelara (ustekinumab; Johnson & Johnson/Mitsubishi Tanabe), as etrolizumab does have head-to-head trials with infliximab and Humira for TNF-alpha inhibitor-naïve patients, and that is being tested in anti-TNF-refractory patients.

- Stelara will likely bypass the G-BA's added benefit assessment in CD as the drug was marketed in Germany for psoriasis and psoriatic arthritis prior to the Act on the Reform of the Market for Medicinal Products (AMNOG; Arzneimittelmarktneuordnungsgesetz). Therefore, the drug will be able to maintain its current pricing level.

A POSITIVE ASSESSMENT FROM THE G-BA WILL IMPACT PRICING NEGOTIATIONS

In Germany, the AMNOG reform was introduced in 2010 with the aim of limiting the cost of pharmaceuticals (GKV-Spitzenverband, 2013). Under this act, pharmaceutical companies must subject new products to an early evaluation of their additional benefit by the G-BA after being launched on the market. The Institute for Quality and Efficiency in Health Care (IQWiG; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) assesses all new medicines for benefit over comparator treatments, and the G-BA considers this assessment before making a final decision.

The G-BA assesses both the extent of added benefit (substantial, considerable [significant], minor, unquantifiable, or added benefit not proven) and the certainty of the benefit (hint, indication, or proof). If it is not possible to prove any additional benefit in relation to a comparator therapy (an existing standard therapy selected by the G-BA), the drug is allocated to a reference price group with comparable active ingredients. Once the G-BA reaches its verdict on the extent of additional benefit, the company enters price negotiations with the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband), where the rebate is negotiated.

If the G-BA is not convinced of the additional benefit provided by a drug, it is unlikely that it will achieve a price that will satisfy the pharmaceutical company if the comparator has a low price. The manufacturer is allowed to keep its list price, while the reimbursed price takes into account the negotiated rebate.

Table 23: **G-BA assessment of key Crohn's disease therapies**

Drug	Probability of added benefit	Extent of benefit	Target patient population	Line of therapy	Comparator	Target patient population size	Notes	Date
Entyvio	No proof	No added benefit	Moderate to severe active CD patients contraindicated, intolerant, or unresponsive to conventional therapy	2+	TNF-alpha inhibitor (Humira or Remicade)	11,000 for CD patients together with patients unsuited for treatment with TNF-alpha inhibitor	No studies submitted	January 2015
Entyvio	No proof	No added benefit	Moderate to severe active CD patients who are contraindicated, intolerant, or unresponsive to TNF-alpha inhibitor treatment	3+	TNF-alpha inhibitor (Humira or Remicade) and prior therapies	n/a	No studies submitted	January 2015

CD = Crohn's disease; TNF = tumor necrosis factor

Source: G-BA, 2015a/b

Table 24: **G-BA assessment of key ulcerative colitis therapies**

Drug	Probability of added benefit	Extent of benefit	Target patient population	Line of therapy	Comparator	Target patient population size	Notes	Date

Table 24: **G-BA assessment of key ulcerative colitis therapies**

Entyvio	No proof	No added benefit	Moderate to severe active UC patients who are contraindicated, intolerant, or unresponsive to conventional therapy	2+	TNF-alpha inhibitor (Humira or Remicade)	5,100 for UC patients together with patients unsuited for treatment with TNF-alpha inhibitor	There were no direct head-to-head studies for the groups of UC patients. The manufacturer submitted an indirect comparison for Entyvio against Humira, with placebo as a common comparator, but the populations assessed were not similar as the studies had different designs. Additionally, the committee stated that the side effects in the Entyvio study were not analyzed correctly	January 2015

Table 24: **G-BA assessment of key ulcerative colitis therapies**

Entyvio	No proof	No added benefit	Moderate to severe active UC patients who are contraindicated, intolerant, or unresponsive to TNF-alpha inhibitor treatment	3+	TNF-alpha inhibitor (Humira or Remicade) and prior therapies	n/a	There were no direct head-to-head studies for the groups of UC patients. The manufacturer submitted an indirect comparison for Entyvio against Humira, with placebo as a common comparator, but the populations assessed were not similar as the studies had different designs. Additionally, the committee stated that the side effects in the Entyvio study were not analyzed correctly	January 2015

Table 24: **G-BA assessment of key ulcerative colitis therapies**

TNF = tumor necrosis factor; UC = ulcerative colitis

Source: G-BA, 2015a/b

LACK OF HEAD-TO-HEAD COMPARISONS RESULTS IN NO ADDED BENEFIT FOR ENTYVIO

Entyvio received evaluations of no added benefit for both UC and CD patients who have failed conventional therapy and also for those refractory to TNF-alpha inhibitors. According to the G-BA, there were no data suitable for an assessment to take place in either of the two indications. Takeda did not submit a dossier of either direct or indirect trials for CD, but submitted adjusted indirect assessments of Humira and Entyvio against placebo as a common comparator for the UC indication. However, as the patient populations in the Entyvio and Humira trials were not sufficiently similar, and the trials had differing designs, the committee could not perform an indirect assessment. The G-BA noted that Entyvio and two of the three Humira studies had two-phase designs, with induction and maintenance phases. In the Entyvio study, patients who entered in the maintenance phase were responders during the induction stage, contrastingly, the maintenance phase of the Humira trials contained both responders and non-responders from the induction phase. Because of the lack of added benefit in the evaluation, Entyvio has to be priced in line with the TNF inhibitors.

CERTAIN SICKNESS FUNDS SUBJECT TNF-ALPHA INHIBITORS TO INDICATIVE BUDGET LIMITS, BUT THE RELEVANCE OF THIS MAY CHANGE UNDER ONGOING REFORMS

In Germany, physicians are subject to indicative prescribing limits or volumes, called Richtgroessen, which are total drug spending limits set at the per-patient level for individual physician specialties, and which are based on drug use, the launches of new treatments, and expected generic entry. They are negotiated each year between physicians' associations and sickness funds. These budget limitations typically act as strong incentives for physicians to prescribe the most cost-effective therapies, as physicians who exceed the limit by 25% must undergo efficiency audits, and if they are unable to explain their higher-than-expected expenditure they are personally liable for the overspend. While such a penalty rarely happens in practice, its possibility is a strong deterrent against excessive drug use. Medicines that achieve Praxisbesonderheit status are exempt from Richtgroessen, and this status confers a competitive advantage to such agents, as physicians can prescribe them without worrying about exceeding the budget limits.

However, with the ongoing reforms in Germany, the statuses of Praxisbesonderheit and Richtgroessen may play lesser roles in market access in the country. Datamonitor Healthcare investigated the Richtgroessen and Praxisbesonderheit rules for Bavaria, Baden-Württemberg, Westfalen-Lippe, Niedersachsen, and Nordrhein – the five largest physicians' associations – and found that for 2017, TNF-alpha inhibitors were not included in the Praxisbesonderheit lists, while only Baden-Württemberg still has Richtgroessen for TNF-alpha inhibitors. Moreover, other associations of statutory insurance physicians (KVs; Kassenärztliche Vereinigungen) are moving towards targeted prescribing quotas.

Table 25: **Spending regulations for TNF-alpha inhibitors in the five largest physicians' associations in Germany**

Association	Richtgroessen?	Praxisbesonderheiten?	Notes
Baden-Württemberg	Yes	No	Gastroenterologists subject to Richtgroessen, €6,595
Bavaria	No	No	No target quotas; biosimilar infliximab is interchangeable with Remicade for existing users
Niedersachsen	No	No	Target quotas, unspecified
Nordrhein	No	No	Prescribing quotas, minimum of 23% for biosimilar prescription
Westfalen-Lippe	No	No	Prescribing quotas. Gastroenterologists must prescribe a minimum of 65% of low-cost or biosimilar TNF-alpha inhibitors such as infliximab, Simponi, or Cimzia. A separate quota exists for infliximab biosimilar of at least 75% of all infliximab prescribed, especially for new patients

Source: KV Baden-Württemberg, 2017; KV Bavaria, 2017; KV Niedersachsen, 2016; KV Nordrhein, 2017; KV Westfalen-Lippe, 2017

A new law passed in 2015 will make it easier for sickness funds to conduct tenders for on-patent drugs, putting pressure on less differentiated brands in competitive markets. The Act to Strengthen Provision in the Statutory Health Insurance System (Gesetz zur Stärkung der Versorgung in der gesetzlichen Krankenversicherung), enacted in June 2015, allows the country's 16 states to replace indicative prescribing amounts with alternative methods of monitoring economical prescribing from 2017 onward. The most likely scenario is that sickness funds will carry out tenders, resulting in the selection of preferred agents in return for discounts. Physicians will then be incentivized to reach determined target volumes of prescription rates of the preferred agents. Furthermore, the list price achieved following AMNOG assessment and pricing negotiations will be less relevant if rebate contracts are put in place.

NEW G-BA SOFTWARE WILL MAKE ADDED BENEFIT ASSESSMENTS AND PRICES FOR COMPETING DRUGS MORE VISIBLE TO PRESCRIBERS

A legislative change passed in March 2017 has paved the way for the introduction of a new prescribing system that may notify physicians when they prescribe drugs with no added benefit in a patient population where a lower-priced alternative exists. Under the Act to Strengthen Pharmaceutical Supply in the Statutory Health Insurance System (Gesetz zur Stärkung der Arzneimittelversorgung in der GKV) – passed in March 2017 and published in May 2017 – the prescribing software will be changed to incorporate the details of AMNOG assessments and to make them visible to prescribers (Bundesrat, 2017). Although the impact of this change on reimbursement is not clear as yet, payers interviewed by Datamonitor Healthcare have asserted that, coupled with

changing efficiency audits, the changes may discourage the prescribing of some drugs in patient subpopulations where added benefit is not proven. This would occur if efficiency audits were changed to state that physicians will be penalized if they are revealed to have prescribed a more expensive drug when there is no added benefit. It is likely that the ruling will pressure physicians to prescribe drugs where an added benefit is given.

If implemented, this tool would mostly impact drugs that have mixed added benefit assessments for some subpopulations and no added benefit in others. The subpopulation analysis is relatively simple for drugs like Entyvio, as it did not receive an added benefit in any of the subpopulations assessed. However, with new approvals and evaluations of added benefit in subpopulations, more restricted access could occur in the future. Datamonitor Healthcare anticipates that as this process continues to evolve, physicians will be more influenced to prescribe medicines only when an added benefit has been assessed.

While this process has yet to be implemented, some payers are optimistic that the system will be in place within a year, whereas others highlight that timescales of two to three years are more likely given the number of different systems in use in the country at present. Furthermore, some payers highlight that the impact of the new prescribing system may be less than expected, as sickness funds are pushing for preferred brand quotas to have a greater impact on the efficiency audits rather than the outcome of the added benefit assessment. Additionally, following the most recent general election in Germany, the future of this new system of efficiency audits is unclear.

"I think this will need at least two years from now. [...] Currently we have 170 different IT system manufacturers for physicians' prescription software, and that is a huge job to implement the G-BA decisions in all these 170 systems. We have to define standards, and all these things they have to program according to these standards, so two to three years from now until it is fully effective out there."

German regional sickness fund payer

"Well, the importance of these subgroups and the new AIS system, so it is really crucial whether a drug has one subgroup without an additional benefit rating and another with a minor. That is quite important. When all subgroups have no additional benefit rating or all have a minor additional benefit rating, easy, but that mix is now more difficult."

German physician association payer

ETROLIZUMAB MAY HAVE MIXED PRICING DUE TO AN ANTICIPATED ADDED BENEFIT IN SOME PATIENT POPULATIONS

German payers interviewed by Datamonitor Healthcare predict that etrolizumab could get a mixed added benefit assessment from the G-BA, dependent upon the target patient population, which would then impact the drug's pricing. Etrolizumab could gain a minor added benefit against infliximab for patients who are naïve to TNF-alpha inhibitors, as the drug is being directly compared to infliximab in the GARDENIA trial using the primary endpoint of sustained remission. Moreover, etrolizumab is also being compared to Humira in the HIBISCUS I and II trials, although clinical remission against the active comparator is only a secondary endpoint. Despite these head-to-head trials, etrolizumab's price is expected to lie between those of biosimilar infliximab and Stelara, which is the most likely comparator for the third-line subgroup in CD.

"It remains at this first line with a chance to get an added benefit [...] superior efficacy versus infliximab [...] for the naïve patients and for the failure patients, it is also a placebo control and placebo is not an option for these patients, they will get Stelara or they get whatever but not placebo. [...] And so there is no additional benefit in the anti-TNF-failure patients with this placebo control.

I think [the price] is a huge negotiation in this case because the Federal Association for Sick Funds will rely on the latest infliximab biosimilar price I think, for the [TNF-naïve] subgroup. For the failure patients, it is easier [and] depends a bit on the adequate comparator. If vedolizumab

and Stelara are the adequate comparators and you have no added benefit, then you can still [have] their price for this subgroup, and the result will be a weighted average between the current Stelara price and the biosimilar price."

German sickness funds payer

STELARA IS EXPECTED TO BYPASS BENEFIT ASSESSMENT IN CD DESPITE APPROVAL POST-AMNOG

German respondents expect that Stelara will not have to go through the G-BA's added benefit assessment process for new active ingredients, as the drug was previously marketed in Germany for psoriasis and psoriatic arthritis. As the G-BA's AMNOG benefit assessment only applies to new active ingredients (G-BA, 2017), Stelara does not qualify. Although the regulations are changing, and as of May 2017 the G-BA can require an assessment for an expanded indication, this is usually limited to drugs with widely varying indications. As such, German payers do not expect that the added CD indication would trigger a new AMNOG assessment. Datamonitor Healthcare anticipates that Stelara will therefore continue to have free pricing in the German market.

"The AMNOG assessment was first launched after 2011, and prior indication extensions do not trigger an AMNOG assessment. There was no, or there is no AMNOG assessment for this new Stelara indication. Since May there is a slightly different situation. Since May, the G-BA can require an assessment if a known drug comes with a new indication, but only if the new indication is very different from the old one, and what does very different mean? This is again not defined by law, [...] but if it's nearby autoimmune disease I do not think it is as new as to justify a full assessment for this drug. Other things, for example like Eylea, one indication in the eye and one for colon carcinoma, that is really different, and if such things would happen for a pre-AMNOG drug this would trigger a new assessment."

German sickness funds payer

"There was a change of law six months ago, and politicians passed a law which now allows the G-BA to assess in-market drugs when they have [...] a completely new indication. But, as we can see, there is some room for interpretation of what is a completely new indication. I would say if the first indication is colon cancer, the second indication is asthma or COPD, that is a completely different indication, but when you would say: 'oh, the first indication was second-line UC, and now it is first-line UC,' I would say that is not a completely new indication. [...] I think [there is] less than a 50% chance to get reviewed."

German physician association payer

"[If AMNOG doesn't happen,] yes, well then nothing happens. Then the free pricing applies and no restrictions."

German physician association payer

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ITALY

INSIGHTS AND STRATEGIC RECOMMENDATIONS

- Delays in pricing and reimbursement decisions from the Italian Medicines Agency (AIFA; Agenzia Italiana del Farmaco) present the greatest barrier to access to inflammatory bowel disease (IBD) medications nationally, with further delays at the regional and local levels. Exemplifying this issue, AIFA has yet to reimburse Stelara (ustekinumab; Johnson & Johnson/Mitsubishi Tanabe) in Crohn's disease (CD), which was approved by the European Medicines Agency in December 2016.

- Access to IBD medications is restricted to specialist use (gastroenterologists), but payers report that budget limits actually play a more important role in restricting access regionally and locally.

- All IBD biologics are reimbursed under "class H: reimbursable" in hospital settings, and are subject to several different access restrictions. In the past, Simponi (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) and Humira (adalimumab; AbbVie/Eisai) were reimbursed under a payment-by-results (PbR) scheme, which has since been removed. Meanwhile, Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) and its biosimilar Inflectra (Pfizer) are subject to AIFA monitoring for pediatric ulcerative colitis (UC), and Humira and Simponi are subject to AIFA monitoring for the adult UC indication. Both groups of drugs are restricted to patients who have Mayo scores of 6–12 and endoscopy scores of 2–3. Additionally, Entyvio (vedolizumab; Takeda) is subject to monitoring for its use in CD, which is limited to patients who have failed on a TNF-alpha inhibitor.

- The regional formulary in Emilia-Romagna follows AIFA access restrictions for IBD medicines. The region further restricts the use of Entyvio in UC to third-line patients, after the failure of a TNF-alpha inhibitor.

DELAYS IN AIFA DECISIONS FOR NEWLY LAUNCHED DRUGS HAMPER REGIONAL AND LOCAL ACCESS

In Italy, AIFA is responsible for both marketing authorizations and pricing and reimbursement decisions on medicines. Pricing and reimbursement negotiations occur concurrently and result in price listing. At the national level, one of the more significant access issues is delays in reimbursement decisions from AIFA for newly launched medications. The impact of national delays is exacerbated by further formulary inclusion delays at the regional and even local (hospital) level, which mean it can be several years before prescribers and patients have access to new drugs. Manufacturers of recently approved or pipeline agents need to be prepared for delays in access and sales that are commonly experienced in Italy, and act as market access barriers as drugs cannot be prescribed until AIFA has determined their pricing and reimbursement. All biologics reviewed by AIFA have had positive reimbursement decisions, with the exception of Stelara for CD, which was approved in December 2016. All drugs reviewed by AIFA are included in the regional formulary of Emilia-Romagna.

LIMITED BUDGETS PRESENT THE GREATEST BARRIER TO BIOLOGICS USE

Payers and physicians interviewed by Datamonitor Healthcare reported that the main access restrictions for IBD medications are regional or hospital budgets for medicines. The drugs must be prescribed by specialists, and the regions determine the specialist

centers where the drugs can be prescribed. This geographical limitation is, however, not considered to be an access barrier. The biggest issue payers and specialists report is the imposed budget restrictions that limit the prescribing of biologics for this group of patients. Some interviewees also report increasing pressure to cut spending as a key threat to future ease of access. Consequently, manufacturers of IBD drugs should prepare for intensified pricing pressures either at the national or regional levels in Italy.

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Table 26: **Reimbursement conditions for Crohn's disease treatments in Italy**

Drug	Decision	Approved target patient population	Line of therapy	Therapeutic innovation?	Reimbursement list (class)	PbR or risk share?	Date of listing	Notes
Entyvio	Restricted	Adults with moderate to severe active CD who have had an inadequate response, or have lost response or intolerant to conventional therapy and TNF-alpha inhibitor	Third	No	H	No	April 2016	Subject to AIFA monitoring registry, which requires failure or contraindication to TNF-alpha inhibitor. Prescription via hospitals or specialist (gastroenterologist, internist) at designated centers. Subject to pharmacovigilance
Humira	Reimbursed	Adults with moderate to severe active CD with contraindication, intolerance, or inadequate response to full course of CSs and/or an immunosuppressant. Children (at least six years old) with moderate to severe active CD with contraindication, intolerance, or inadequate response to conventional therapy (primary nutritional therapy and CS and/or an immunomodulator)	Second or later	No	H	No	July 2016	Prescription via hospitals or specialist (rheumatologist, dermatologist, gastroenterologist, internist, pediatrician)

Table 26: **Reimbursement conditions for Crohn's disease treatments in Italy**

Remicade	Reimbursed	Adults with moderate to severe active CD who have not responded to a full and adequate course of CS and/or an immunosuppressant, or in patients intolerant to such therapies or who have contraindications. Adults with fistulizing active CD who have not adequately responded to a complete cycle of conventional therapy (antibiotics, drainage, and immunosuppressive therapy). Children at least six years old with severe active CD who have had an inadequate response to conventional therapy, including primary nutritional therapy and therapy with a CS and/or an immunomodulator, unless intolerant or contraindicated	Second or later	No	H	No	August 2014	Prescription via hospitals or specialist (gastroenterologist, internist)
Stelara	n/a	Adults with moderate to severe active CD who have had an inadequate response, loss of response, or intolerant to conventional therapy or to a TNF-alpha inhibitor, or contraindicated to therapies	n/a	n/a	C(nn)	n/a	August 2017	Subject to risk management plan and pharmacovigilance. Manufacturer must produce educational information for health professionals and patients. Hospital medicine only

Note: Reimbursement class: C(nn) = not yet assessed by AIFA; H = reimbursed – distributed by hospitals

AIFA = Italian Medicines Agency; CD = Crohn's disease; CS = corticosteroid; PbR = payment by results; TNF = tumor necrosis factor

Source: Gazzetta Ufficiale, 2001; 2016a/c; 2017

Table 27: **Reimbursement conditions for ulcerative colitis treatments in Italy**

Drug	Decision	Approved target patient population	Line of therapy	Therapeutic innovation?	Reimbursement list (class)	PbR or risk share?	Date of listing	Notes
Entyvio	Reimbursed	Adults with moderate to severe active UC, with inadequate response, lost response, or are intolerant to conventional therapy or TNF-alpha inhibitor	Second or later	No	H	No	April 2016	Prescription via hospitals or specialist (gastroenterologist, internist). Subject to pharmacovigilance
Humira	Reimbursed	Adults with moderate to severe active UC who have had an inadequate response to conventional therapy (CS and 6-MP or AZA) or who are intolerant or contraindicated	Second or later	No	H	No (previously yes)	July 2016	Subject to AIFA monitoring registry, but PbR scheme has been removed. Prescription via hospitals or specialist (gastroenterologist, internist, pediatrician)

Table 27: **Reimbursement conditions for ulcerative colitis treatments in Italy**

Remicade	Reimbursed	Adults with moderate to severe active UC who have had an inadequate response to conventional therapy (CS and 6-MP or AZA), or who are intolerant or contraindicated. Children and adolescents (6–17 years old) with severe active UC who have not adequately responded to conventional therapy (CS and 6-MP or AZA), or who are intolerant or contraindicated	Second or later	No	H	No	August 2014	Subject to AIFA monitoring registry (pediatric UC) at specialist centers. Prescription via hospitals or specialist (gastroenterologist, internist)

Table 27: **Reimbursement conditions for ulcerative colitis treatments in Italy**

Simponi	Reimbursed	Adults with moderate to severe active UC who have experienced an inadequate response to conventional therapy (CS and 6-MP or AZA), or who are intolerant or contraindicated	Second or later	No	H	No (previously yes)	January 2015	Subject to AIFA monitoring registry, but PbR scheme has been removed. Prescription via hospitals or specialist (gastroenterologist, internist)

Note: Reimbursement class: H = reimbursed – distributed by hospitals

6-MP = mercaptopurine; AIFA = Italian Medicines Agency; AZA = azathioprine; CS = corticosteroid; PbR = payment by results; TNF = tumor necrosis factor; UC = ulcerative colitis

Source: Gazzetta Ufficiale, 2014; 2015; 2016b/d

AIFA REIMBURSES ALL BIOLOGICS APPROVED FOR CD AND UC, BUT WITH ACCESS RESTRICTIONS

With the exception of Stelara in CD, which has yet to be reviewed, AIFA has reimbursed all biologics approved for CD and UC, but each drug faces access restrictions. All biologics approved are categorized under class H, which are 100% reimbursed in the hospital setting. In the past, Simponi and Humira were reimbursed under a PbR scheme, but this has now been removed. Remicade and Inflectra are subject to AIFA monitoring for pediatric UC, while Humira and Simponi are subject to monitoring registries for the adult UC indication. Both groups of drugs are restricted to patients who have Mayo scores of 6–12 and endoscopy scores of 2–3. Additionally, Entyvio is subject to monitoring for its use in CD (AIFA, 2017).

AIFA monitoring registries are the most complete process to capture data on expenditure and ensure appropriateness of use of medications eligible for reimbursement. Prescriptions for these drugs must be made through authorized centers via the web-based monitoring system, with physicians having to complete online prescription forms that include the patient's name, indication, and dosing information. The system then validates the prescription and requests the hospital to release the medicine (AIFA, nd). Although the monitoring presents an administrative barrier to access, patients can still obtain treatment provided use coincides with the reimbursement criteria for the drug. The use of monitoring registries signals the significance of UC and CD to Italian payers, and the consequent high level of spending on these biologics. Datamonitor Healthcare expects that payers will be looking closely at physician prescriptions and the use of these medications to ensure appropriate prescribing.

AIFA restricts Entyvio use in CD to patients refractory to TNF-alpha inhibitors

Despite attaining marketing authorization for use in adults with moderate to severe active CD with inadequate response (loss of response or intolerance) to conventional therapy or TNF-alpha inhibitors, Entyvio is restricted nationally to a third-line option, for patients refractory to TNF-alpha inhibitors. Moreover, Entyvio's monitoring registry blocks reimbursement for patients with a score of less than eight on the Harvey-Bradshaw index, which is a modified Crohn's Disease Activity Index scoring system. Specialists can prescribe Entyvio as a first-line biologic if patients have moderate to severe heart failure, are aged 65 years or older with significant signs of co-morbidity, if they have tested positive for a hepatitis B virus infection, if they require live vaccine administration, or if they have a high risk of malignant neoplasia, or latent tuberculosis (TB) (AIFA, 2017).

UC AND CD DRUGS REIMBURSED BY AIFA ARE FOUND IN THE REGIONAL FORMULARY OF EMILIA-ROMAGNA

Currently, all UC and CD drugs reimbursed by AIFA are found in the Italian regional formulary of Emilia-Romagna. However, given increasing budgetary pressures, some regional decision-makers have enacted formulary access restrictions such as narrowing the patient populations eligible for therapy.

Table 28: **Italian regional formulary decisions for Crohn's disease drugs**

	Emilia-Romagna	
Drug	On formulary?	Note
Entyvio	Yes	For specialist use only
Humira	Yes	For specialist use only
Remicade	Yes	For specialist use only. RMP
Stelara	Not reviewed	n/a
RMP = risk management plan		

Source: Regione Emilia-Romagna, 2017a

Table 29: **Italian regional formulary decisions for ulcerative colitis drugs**

	Emilia-Romagna	
Drug	On formulary?	Note
Entyvio	Yes	For specialist use only. Restricted to third line. PTR
Humira	Yes	For specialist use only
Remicade	Yes	For specialist use only. RMP
Simponi	Yes	For specialist use only
PTR = regional therapeutic plan; RMP = risk management plan		

Source: Regione Emilia-Romagna, 2017a

Emilia-Romagna restricts Entyvio's use in UC to after failure with TNF-alpha inhibitors

Despite attaining marketing authorization and AIFA reimbursement for use in adults with moderate to severe active UC with inadequate response (loss of response or intolerance) to conventional therapy or TNF-alpha inhibitors, Entyvio's use in UC is restricted in Emilia-Romagna to patients refractory to TNF-alpha inhibitors. The committee cites the absence of a direct comparative

trial between Entyvio and TNF-alpha inhibitors, and the submission of one single regression study, along with incomparable safety data, as the reasoning for the placement only later in the treatment pathway. Specialists can still prescribe Entyvio as a first-line biologic, but doing so should be done on a case-by-case basis while assessing the benefits and risks of the therapy. Conditions such as contraindication or intolerance to TNF-alpha inhibitors, and patients with latent TB, may be reasons for giving Entyvio as a first-line therapeutic (Emilia-Romagna, 2017b).

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SPAIN

INSIGHTS AND STRATEGIC RECOMMENDATIONS

- The Spanish Agency of Medicines and Medical Devices (AEMPS; Agencia Española de Medicamentos y Productos Sanitarios) has produced therapeutic positioning reports (IPTs; Informes de posicionamiento terapéutico) for inflammatory bowel disease (IBD) medications Entyvio (vedolizumab; Takeda) in ulcerative colitis (UC) and Crohn's disease (CD), and Stelara (ustekinumab; Johnson & Johnson/Mitsubishi Tanabe) in CD. The non-TNF-alpha inhibitors are restricted to after failure with TNF-alpha inhibitors, but both Entyvio in UC and Stelara in CD are considered as therapeutic alternatives to TNF-alpha inhibitors when a patient is contraindicated to the latter class of drugs. Entyvio in CD is not considered to be a therapeutic alternative due to its modest efficacy results in indirect comparisons with other TNF-alpha inhibitors.

- The Catalonian therapeutics committee considers TNF-alpha inhibitors as first-line biologic options in patients with moderate to severe CD. Consistent with IPTs, Entyvio is considered to be a second-line biologic, to be used when patients are contraindicated, intolerant, or have failed TNF-alpha inhibitor therapy. Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) is the biologic of choice for patients with fistulizing CD.

- Due to a lack of head-to-head trials, the Andalusian therapeutics committee considers Humira (adalimumab; AbbVie/Eisai) and Remicade to be therapeutically equivalent alternatives for patients with severe CD who have failed conventional therapy.

- In some regions, reimbursement for IBD drugs could move towards a flat per patient fee, where an allocated monthly spending limit will be enforced. This new payment mechanism may compel physicians to use the least expensive therapy to ensure their hospital does not exceed spending thresholds, and will put further pricing pressures onto manufacturers.

NATIONAL REIMBURSEMENT DECISIONS ARE USUALLY NOT A BARRIER TO ACCESS

In Spain, pricing and reimbursement decisions are made at the national level by the Interministerial Commission of Medicine Prices and the Directorate of Pharmaceutical and Health Products. Pricing discussions and reimbursement negotiations occur at the same time. Since 2013, pricing and reimbursement decisions for new medicines have been influenced by IPTs, which are produced by the AEMPS. The organization usually conducts IPT assessments before regions and local hospitals commit to their own evaluations, although exceptions can occur. For IBD, the AEMPS has conducted IPT assessments only for Entyvio and Stelara, leaving formulary decisions to regional authorities.

Table 30: **Therapeutic positioning reports for IBD drugs in Spain**

Indication	Drug	Decision	Approved target patient population	Line of therapy	Added therapeutic benefit?	Summary of review
UC	Entyvio	Restricted	Moderate to severe active UC patients who are contraindicated, intolerant, or have failed treatment with conventional therapy or with anti-TNF-alpha inhibitor drugs	2+	No	Entyvio is an alternative therapy approved for inducing and maintaining treatment in patients with moderate to severe UC who have failed therapy with anti-TNF-alpha inhibitor drugs or with other conventional therapies. Reimbursement is restricted to third line (after failure with TNF-alpha inhibitor) unless intolerant or contraindicated

Table 30: **Therapeutic positioning reports for IBD drugs in Spain**

CD	Entyvio	Restricted	Moderate to severe active CD in patients who are contraindicated, intolerant, or have failed treatment with conventional therapy or TNF-alpha inhibitor therapy	3+	No	Due to modest efficacy, Entyvio cannot be considered as an alternative for patients with CD, as the medicine's induction and remission of disease are delayed compared to other biologic options. Entyvio could be used in patients with limited therapeutic alternatives who are contraindicated, intolerant, or have failed TNF-alpha inhibitor treatment. Reimbursement is restricted to third line (after failure with TNF-alpha inhibitor) unless intolerant or contraindicated

Table 30: **Therapeutic positioning reports for IBD drugs in Spain**

CD	Stelara	Restricted	Adults with moderate to severe active CD who have had an inadequate response, loss of response, or intolerant to conventional treatment or TNF-alpha inhibitor, or are contraindicated to the treatment	3	No	Stelara is reimbursed for adults with moderate to severe active CD who have had an inadequate response, presented with a loss of response, or are intolerant to conventional treatment and TNF-alpha inhibitors, or as an alternative when patients are contraindicated to anti-TNF-alpha molecules. Stelara is an alternative for these patients and is viewed as having a faster onset of action compared to Entyvio

CD = Crohn's disease; TNF = tumor necrosis factor; UC = ulcerative colitis

Source: AEMPS, 2015, 2017

IPT RESTRICTS ENTYVIO IN UC AND CD TO PATIENTS WHO HAVE FAILED TNF-ALPHA INHIBITORS

The AEMPS assessment of Entyvio restricts reimbursement of the drug to patients in the third line after failure with TNF-alpha inhibitors, unless they are contraindicated or intolerant. Despite acknowledging that Entyvio is a therapeutic alternative for inducing and maintaining remission in UC patients, due to its comparable clinical performance to the TNF-alpha inhibitors, the AEMPS implemented this restriction due to a lack of head-to-head comparisons.

For CD patients, the committee notes that Entyvio is not a therapeutic alternative due to the modest efficacy of the drug demonstrated in indirect comparisons with TNF-alpha inhibitors. Entyvio seems to have delayed timing in inducing remission compared to other biologics, and would be a disadvantage for patients requiring rapid remission. The committee, however, acknowledges that as there are a limited number of therapies available, the drug could be considered as an option in patients contraindicated or intolerant to TNF-alpha inhibitors (AEMPS, 2015). Datamonitor Healthcare anticipates that reimbursement restrictions for Entyvio will greatly impact its market uptake in Spain, as regional decision-makers will follow the AEMPS recommendations in this instance.

IPT RESTRICTS STELARA FOR CD TO PATIENTS WHO HAVE FAILED ON OR WHO ARE CONTRAINDICATED TO TNF-ALPHA INHIBITORS

The AEMPS also restricts reimbursement of Stelara to patients who have had an inadequate response to conventional therapy and a TNF-alpha inhibitor, unless the patient is contraindicated to the latter, despite Stelara's approval in line with anti-TNF-alpha drugs. Stelara has demonstrated superiority against placebo for the induction of clinical response at week 6 in both naïve and anti-TNF-failure or anti-TNF-intolerant patients. However, in the maintenance phase of the study, nearly 40% of patients who were responsive to Stelara during the induction phase lost response after week 44 of being treated with placebo.

In the absence of head-to-head trials, payers say that it cannot be concluded that the efficacy of Stelara is stronger than that of TNF-alpha inhibitors. The committee states, however, that for patients who have failed or are contraindicated to TNF-alpha inhibitors, Stelara is an alternative, and that it provides a faster onset of action compared to Entyvio (AEMPS, 2017). Datamonitor Healthcare anticipates that although Stelara is restricted to the third line, it is viewed more favorably than Entyvio, which may push the integrin-based antibody further down the treatment pathway.

REGIONAL ACCESS TO UC AND CD TREATMENTS VARIES IN SPAIN

Budget pressures experienced in many of the Spanish autonomous regions have resulted in variation in access to treatments. While pricing and reimbursement decisions are made at the national level, autonomous regions are tasked with paying for the treatments and often carry out their own reassessments.

The New Evaluation Group, Standardization and Drug Selection Research (GENESIS; Grupo de Evaluación de Novedades, Estandarización e Investigación en Selección de Medicamentos) group is also a key force in assessments of new drugs used in inpatient and outpatient hospital settings. The group originated from a need for greater coordination and collaboration among pharmacists in the drug selection process, and is part of the working group of the Spanish Society of Hospital Pharmacy (SEFH; Sociedad Española de Farmacia Hospitalaria). GENESIS produces and compiles regional and local assessments for hospital and outpatient drugs. The program is currently the reference system used by a significant percentage of centers for the documentation and evaluation of new medicines for Spanish hospitals.

GENESIS assesses drugs for hospital use using the method for assistance in making decisions and writing drug evaluation reports

(MADRE; Método de Ayuda para la toma de Decisiones y la Realización de Evaluaciones de Medicamentos). This system gives ratings of A–E to recommend exclusion, inclusion, or inclusion with restrictions for drugs in the hospital formulary (GFT; Guía Farmacoterapéutica).

Datamonitor Healthcare has analyzed MADRE assessments produced and compiled by GENESIS, the Consell Assessor de Medicació Hospitalària de Dispensació Ambulatòria (CAMHDA), Grupo Hospitalario de Evaluación de Medicamentos de Andalucía (GHEMA), and the Andalusian hospital formulary guideline (GFTHA; Guía Farmacoterapéutica de Hospitales de Andalucía).

Table 31: **Spanish Society of Hospital Pharmacy ratings**

Rating	Included in the GFT?	Reasons/conditions
A0	No	Absence of basic requirements
A1	No	Insufficient information regarding the drug
A2	No	Not necessary to be used in hospitals
B1	No	Insufficient evidence of safety and efficacy compared to current treatment
B2	No	Worse safety and efficacy profiles compared to current treatment
C1	No	The drug has comparable safety and efficacy to other alternatives, but does not provide improvement in cost effectiveness nor the possibility of cost-management advantages
C2	Yes	For the indication, the drug has comparable efficacy and safety to alternatives and does not provide improvement in cost effectiveness. However, joint purchasing procedures could aid in managing cost of the drug. It is considered a therapeutic equivalent, and the drug will exist as a choice during the public procurement procedure
D1	Yes	With specific recommendations
D2	Yes	With specific recommendations and commitment to reassessment
E	Yes	Included without specific recommendations
GFT = pharmaceutical guide		

Source: Junta de Andalucía, 2013

Table 32: **Regional MADRE assessments for Crohn's disease drugs**

Drug	Region/assessor	Rating	Comparator	Target patient population	Summary
Entyvio	GENESIS-SEFH	D1	n/a	Patients with moderate to severe active CD who are contraindicated or intolerant, or failed with conventional therapy or TNF-alpha inhibitors	Restricted to third-line treatment after failure with TNF-alpha inhibitor (follows AEMPS). Comparator used in clinical trials was placebo, and although Entyvio demonstrated superiority against the comparator, Remicade and Humira are established standard of care for moderate to severe active CD after failure with conventional therapy, and both have achieved rapid remission. The efficacy of Entyvio on induction is modest in general. Cost-effectiveness analysis was not performed as there was no price during the assessment period. The committee believes, however, that the price is more expensive than infliximab or adalimumab
Humira	Andalusia	C2	Remicade	Patients with severe active CD who have not responded to complete and adequate therapy with CSs and/or immunosuppressants, or who are intolerant or contraindicated to these drugs	Humira is considered as an ATE to Remicade. In patients who are TNF-alpha inhibitor-naïve, the annual treatment cost for Remicade is almost double that with Humira. In patients who have failed Remicade treatment, Humira adds an additional incremental cost of €91,289 in this patient population, but is the only alternative proven to be effective, and manages to statistically increase the number of patients in remission
Remicade	Andalusia	D1	n/a	Severe active CD refractory to CS and immunosuppressant. Patients with fistulizing CD refractory to conventional treatment	Patients with severe and active disease, refractory to other treatments

AEMPS = Spanish Agency of Medicines and Medical Devices; ATE = therapeutically equivalent alternative; CD = Crohn's disease; CS = corticosteroid; TNF = tumor necrosis factor

Source: GENESIS-SEFH, 2015a; Junta de Andalucía, 2007; nd

Table 33: **Regional MADRE assessments for ulcerative colitis drugs**

Drug	Region/assessor	Rating	Comparator	Target patient population	Summary
Entyvio	GENESIS-SEFH	D1	n/a	Patients with moderate to severe active UC who are contraindicated or intolerant, or failed with conventional therapy and TNF-alpha inhibitors	Reimbursement is restricted to third line (consistent with AEMPS)
Simponi	Andalusia	n/a	TNF-alpha inhibitors	Adults with moderate to severe UC who are naïve to biological agents	Simponi demonstrated superiority to placebo in patients naïve to biologic treatment, but there are no clinical trials among the TNF-alpha inhibitors. Indirect comparisons suggest that all three TNF-alpha inhibitors are valid alternatives. Simponi also has a similar tolerability profile compared to other TNF-alpha inhibitors. Its SC administration every four weeks may be more convenient than other options. Treatment with Simponi over two years may be less cost effective than other alternatives

AEMPS = Spanish Agency of Medicines and Medical Devices; SC = subcutaneous; TNF = tumor necrosis factor; UC = ulcerative colitis

Source: GENESIS-SEFH, 2015b; Junta de Andalucía, 2014

colitis drugs

THE CATALONIAN THERAPEUTICS COMMITTEE HAS OUTLINED A PATHWAY FOR CD

The Catalonian therapeutics committee has stated its position on the therapeutic pathway for Remicade, Humira, and Entyvio for patients with moderate to severe CD, and also for patients with fistulizing pathology. For moderate to severe CD, TNF-alpha inhibitors are considered as the first-line biologics, with Remicade and Humira as therapeutic alternatives to one another. As there are no head-to-head trials to determine efficacy or safety differences between the two TNF options, the committee recommends the most economically cost-effective option to be used first. Entyvio is considered to be a second-line option among biologics, when patients are contraindicated, have lost response, or are intolerant to TNF-alpha inhibitors. This is consistent with the AEMPS recommendation to reimburse only patients refractory to TNF-alpha inhibitors. For patients with a fistulizing pathology, Remicade is the treatment of choice (Generalitat de Catalunya, 2017).

Andalusia determines “alternative therapeutic equivalence” status for Remicade and Humira in severe CD

The Andalusian therapeutic committee considers Humira as a therapeutic equivalent to Remicade in patients with severe CD who have failed conventional therapy. In the absence of head-to-head trials demonstrating superior efficacy, Humira and Remicade are differentiated mostly in their mode of administration, but do not have significant improvement in reducing symptoms. At the time of review, Humira was the only available choice for patients who had failed treatment with Remicade. Humira is also nearly half the cost of Remicade (Junta de Andalucía, 2007). Datamonitor Healthcare anticipates that the statuses of these drugs will engender pricing competition among manufacturers to gain preferred status in individual hospitals.

MOVING TOWARDS A FLAT FEE PER PATIENT WILL INCENTIVIZE USE OF THE LEAST EXPENSIVE IBD THERAPY

In some regions, Spanish payers comment that IBD drugs will be subject to allocated monthly spending limits, as has occurred in other indications, and this may result in use of the least expensive therapy. Datamonitor Healthcare anticipates that monthly spending limits will encourage further competition among both first-line and second-line medications, and will drive use of the most cost-effective options in each line of therapy, including biosimilars. Manufacturers will need to ensure that the cost of their medications falls below this threshold in order to effectively compete in the Spanish market.

“In each disease, we have an amount that the CatSalut, who is the payer, pays us. For instance, for arthritis they pay I think around 800 euros per patient per month, and in the case of gastroenterology diseases they pay 1,108 euros per patient per month. It is different, and psoriasis also has a different reimbursement index.”

Spanish regional payer

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UK

INSIGHTS AND STRATEGIC RECOMMENDATIONS

- The National Institute for Health and Care Excellence (NICE) has performed single technology appraisals (TAs) for the Crohn's disease (CD) drugs Entyvio (vedolizumab; Takeda) and Stelara (ustekinumab; Johnson & Johnson/Mitsubishi Tanabe), and multiple technology assessments (MTAs) for Humira (adalimumab; AbbVie/Eisai) and Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe). For ulcerative colitis (UC), NICE conducted single TAs for Remicade and Entyvio, and an MTA for Remicade, Humira, and Simponi (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe). Treatment with biologics is recommended to be reassessed after 12 months, or upon treatment failure, and treatment should also be discontinued for patients in clinical remission. Patients may be restarted on therapy after treatment failure due to withdrawal.

- Entyvio is restricted to the third line in CD after failure with a TNF-alpha inhibitor, and is only cost effective after a patient access scheme (PAS) consisting of a simple discount. The drug is not considered to be a cost-effective use of National Health Service (NHS) resources in second-line use.

- Stelara's faster onset of action, more convenient dosing, inexpensive intravenous (IV) loading dose, and more favorable NICE recommendation provide the drug with advantages over Entyvio in CD. Stelara has attained reimbursement in line with the TNF-alpha inhibitors, while Entyvio is only reimbursed after TNF-alpha inhibitor failure. Although Stelara is unlikely to be used in line with the TNF-alpha inhibitors in clinical practice, it could potentially push Entyvio further down the therapeutic pathway.

- Entyvio attained reimbursement in UC in line with its marketing authorization following the agreement of a PAS and a one-year stopping rule. NICE asserts that as long as both conditions are applied, Entyvio could be used in patients both naïve to TNF-alpha inhibitors and those who are refractory.

- Remicade is reimbursed for adolescent and pediatric patients with severe UC despite not meeting the cost-effectiveness threshold, due to uncertainties around the cost and uncaptured quality-adjusted life year (QALY) benefits. Access to Remicade for pediatric UC patients is unlikely to be impeded in the UK market.

- Xeljanz's (tofacitinib; Pfizer) price will hinge on the target price Pfizer aims for in rheumatoid arthritis (RA), as this indication is more prevalent than UC. Payers expect also that Xeljanz's price will be influenced by that of Olumiant (baricitinib; Eli Lilly/Incyte), the first Janus kinase (JAK) inhibitor to launch in the UK. Pfizer will need to concede to discounts as Olumiant was launched at a lower price than TNF-alpha biosimilars. Without a lower price, Xeljanz will be relegated to later lines of therapy.

NICE APPROVAL IS A KEY MARKET ACCESS BARRIER

Gaining a positive recommendation from the UK's NICE health technology assessment watchdog is a key step in securing market access in England. In Scotland, the Scottish Medicines Consortium (SMC) carries out faster and simpler assessments of new technologies (compared to NICE), and its decisions are binding across the Scottish NHS.

NICE conducts comprehensive TAs, and provides evidence-based technical and economic evaluations of selected drugs that require compliance from clinical commissioning groups (CCGs), NHS England, and local authorities within three months of publication. The cornerstone of NICE's evaluations is the incremental cost-effectiveness ratio (ICER), defined as the increase in costs of using a new

medicine over a comparator divided by the increase in health benefits (measured in QALYs gained). The cost-effectiveness threshold usually used by NICE is in the range of £20,000 ($27,104) to £30,000 ($40,656). Medicines with an ICER above this threshold are usually not recommended for use on the NHS (Claxton et al., 2013).

NICE has performed single TAs in inflammatory bowel disease (IBD), and gave positive recommendations to Remicade, Humira, Simponi, and Entyvio in adult UC, Remicade in pediatric UC, and Remicade, Entyvio, and Humira in CD. These binding documents require the NHS to make these approved drugs available within local formularies. Payers comment, however, that while guidelines assist in determining appropriate therapies, clinicians have the final say in determining the course of treatment, as long as they have NICE support for use in a particular line of therapy.

Table 34: **NICE assessments of key Crohn's disease therapies**

Drug	Decision	Target patient population	Line of therapy	Comparator	ICER	Reasons	Restriction	PAS?	Date of TA

Table 34: **NICE assessments of key Crohn's disease therapies**

Entyvio	Restricted (patient population, PAS)	Adults with moderate to severe active CD unresponsive or intolerant to either conventional therapy or TNF-alpha inhibitor	2+	TNF-alpha inhibitor or conventional non-biological therapy	TNF-alpha inhibitor-naïve: TNF-alpha inhibitor vs Entyvio: Dominated; TNF-alpha inhibitor-failure: Entyvio vs conventional nonbiological therapy: £21,600 per QALY gained	Entyvio is considered cost effective when used in patients who have failed therapy with a TNF-alpha inhibitor, but is not recommended for patients who are TNF-alpha inhibitor-naïve. The committee considers Entyvio as an innovative drug due to the gut-selective novel mechanism of action, which may result in a better safety profile	Failure, contraindication, or intolerance to TNF-alpha inhibitor; PAS – discount on list price	Yes	August 2015

Table 34: **NICE assessments of key Crohn's disease therapies**

Humira, Remicade	Recommended	Adults with severe active CD unresponsive, intolerant, or contraindicated to conventional therapy (immunosuppressive and/or CS treatments)	2+	Standard of care	Most accepted ICER (lifetime horizon): At one year – Remicade vs standard of care: £19,050 per QALY gained; Humira vs standard of care: £7,190. After two years – Remicade vs standard of care: £21,300 per QALY gained; Humira vs standard of care: £10,310	There was a large discrepancy between the manufacturer's model and assessment group model due to sources of data used. Continuous use for defined periods in patients responsive to induction treatment is cost effective. However, there is considerable uncertainty regarding clinical and cost effectiveness of both drugs over periods longer than one year	n/a	No	May 2010

Table 34: **NICE assessments of key Crohn's disease therapies**

Remicade	Recommended	Active fistulizing CD unresponsive, contraindicated, or intolerant to conventional therapy (antibiotics, drainage, and immunosuppressive treatments)	2+	Standard of care	Manufacturer's ICER – Remicade (maintenance) vs standard of care: £30,300 per QALY gained; Assessment group ICER – Remicade (maintenance) vs standard of care: £193,328 per QALY gained; Remicade (induction) vs standard of care: Dominated	Large discrepancy between manufacturer's model and assessment group model. Although the ICER is relatively high, NICE recommended Remicade due to the severity and dearth of treatment options for this population	n/a	No	May 2010

Table 34: **NICE assessments of key Crohn's disease therapies**

Remicade	Recommended	Patients aged 6–17 years with severe active CD unresponsive, contraindicated, or intolerant to conventional therapy (CS, immunomodulators, and primary nutrition therapy)	2+	Standard of care	Manufacturer's ICER – Remicade (maintenance) vs standard of care: £13,891 per QALY gained	Assessment group did not conduct ICER analysis. Despite concerns from assessment group regarding ICER, children and young people could benefit more from treatment than adults. There are greater potential lifelong effects on QoL and avoiding potential toxicity from alternative therapies	n/a	No	May 2010

Table 34: **NICE assessments of key Crohn's disease therapies**

Stelara	Recommended	Adults with moderate to severe active CD with inadequate response, lost response, or were intolerant or contraindicated to conventional therapy or TNFalpha inhibitor	2+	Standard-of-care biologics	Manufacturer's ICER base case analysis – Stelara vs standard of care with biologics: Dominated; Assessment group considered a cost-minimization analysis most appropriate given small differences in QALY gains between biologics	Cost minimization from the company analysis, which used a confidential pricing arrangement, demonstrated lower total costs at year one compared to other biologic treatments at the list price. However, different prices could be available in the NHS for these comparator treatments, and therefore physicians need to take into account the total cost of treatment when	Discount agreed with CMU	No	July 2017

Table 34: **NICE assessments of key Crohn's disease therapies**

						prescribing			

Note: for all therapies, stop therapy upon failure, or when surgery is needed, or after 12 months of treatment, whichever occurs first. Continue only with evidence of benefit. Consider discontinuing treatment for patients in stable clinical remission. Relapsing patients after treatment holiday may have the option to be retreated.

CD = Crohn's disease; CMU = Commercial Medicines Unit; CS = corticosteroid; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PAS = patient access scheme; QALY = quality-adjusted life year; QoL = quality of life; SOC = standard of care; TA = technology assessment

Source: NICE, 2010; 2015c; 2017

Table 35: **NICE assessments of key ulcerative colitis therapies**

Drug	Decision	Target patient population	Line of therapy	Comparator	ICER	Notes	Restriction	PAS?	Date of TA
Entyvio	Restricted (PAS)	Adults with moderate to severe UC with inadequate response to TNF-alpha inhibitor treatment	3+	Conventional therapy	Entyvio vs conventional therapy (Swinburn et al.): £27,500; Entyvio vs conventional therapy (Woehl et al.): £31,900; Entyvio vs conventional therapy (base-case utilities): £37,000	Entyvio is considered innovative. The benefit of targeted immunosuppression might not be fully captured in the model. Additionally, the published utility values resulted in an ICER that is in the upper limit for cost effectiveness	PAS – simple discount to list price	Yes	June 2015

Table 35: **NICE assessments of key ulcerative colitis therapies**

Entyvio	Restricted (PAS)	Adults with moderate to severe UC naïve to TNF-alpha inhibitor treatment	2+	Humira or conventional therapy	Entyvio vs Humira: £7,000 per QALY gained; Entyvio vs conventional therapy: £5,000 per QALY gained	Entyvio is considered innovative. Assuming a one-year stopping rule and using Swinburn et al. rather than Woehl et al. utility values, Entyvio's ICER is less than £20,000 per QALY gained relative to comparators, and is therefore more effective and less costly	PAS – simple discount to list price	Yes	June 2015

Table 35: **NICE assessments of key ulcerative colitis therapies**

Humira, Remicade, Simponi	Recommended	Adults with moderate to severe UC with inadequate response or are contraindicated or intolerant to conventional therapy (CS and 6-MP or AZA) and for whom colectomy is an option	2+	Colectomy	Colectomy vs any TNF-alpha inhibitor or conventional therapy: Dominated	Colectomy provides 14.72 QALYs at a cost of £41,921. At ICERs of £20,000 and £30,000 per QALY gained, colectomy had a 97% and 96% chance of being cost effective, respectively. TNF-alpha inhibitors had a 0% chance of being cost effective compared with colectomy. Despite this, the drugs are used in line with marketing authorization, as the analysis underestimated the cost effectiveness of TNF-alpha	PAS (Simponi only) – 100mg dose at 50mg price	Yes	February 2015

Table 35: **NICE assessments of key ulcerative colitis therapies**

						inhibitors			
Humira, Remicade, Simponi	Recommended	Adults with moderate to severe UC with inadequate response or are contraindicated or intolerant to conventional therapy (CS and 6-MP or AZA) and for whom colectomy is not an option	2+	Compared to each other and conventional therapy	Humira vs Remicade: Dominated, with QALY 0.01; Humira vs conventional therapy: £50,624 per QALY gained; Humira vs Simponi: Extendedly dominated; Simponi vs conventional therapy: £97,149 per QALY gained	At an ICER of £20,000 per QALY gained, Humira could not be cost effective vs conventional therapy. At an ICER of £30,000 per QALY gained, chance rose to 5%. Despite this, the drugs were accepted in line with marketing authorization as the committee felt that the analysis underestimated the cost effectiveness of TNF-alpha inhibitors	PAS (Simponi only) – 100mg dose at 50mg price	Yes	February 2015

Table 35: **NICE assessments of key ulcerative colitis therapies**

Remicade	Recommended	Patients 6–17 years old with inadequate response or contraindicated or intolerant to conventional therapy (CS and 6-MP or AZA) and for whom colectomy is an option	2+	Colectomy	Colectomy vs Remicade: Dominated	There was a 0% chance that Remicade is cost effective compared to colectomy at an ICER of £20,000 per QALY gained. Despite this, the drug was accepted in line with marketing authorization as the committee felt that the analysis underestimated the cost effectiveness of TNF-alpha inhibitors	n/a	No	February 2015

Table 35: **NICE assessments of key ulcerative colitis therapies**

Remicade	Recommended	Patients 6–17 years old with inadequate response or contraindicated or intolerant to conventional therapy (CS and 6-MP or AZA) and for whom colectomy is not an option	2+	Conventional therapy	Remicade vs conventional therapy: £68,400 per QALY gained (QALYs: 0.34; cost: £23,268)	There was a 0% chance that Remicade is cost effective compared to conventional therapy at an ICER of £20,000 per QALY gained. Despite this, the drug was accepted in line with marketing authorization as the committee felt that the analysis underestimated the cost effectiveness of TNF-alpha inhibitors	n/a	No	February 2015

Table 35: **NICE assessments of key ulcerative colitis therapies**

Remicade	Restricted (patient population)	Patients with acute exacerbations of severe active UC	2+	Cyclosporine	All patients – Remicade vs cyclosporine: £48,400 after correction to the model regarding percentage of patients on colectomy between four and 12 months; Patients contraindicated to cyclosporine – Remicade vs standard care: £11,600 per QALY gained; Remicade vs immediate surgery: £13,400 per QALY gained	Remicade is not more clinically or cost effective than cyclosporine, and should not be used in patients for whom cyclosporine is suitable. However, the committee felt that in patients intolerant to cyclosporine, Remicade would be a cost-effective use of NHS resources	Patients contraindicated or intolerant to cyclosporine	No	December 2008

Table 35: **NICE assessments of key ulcerative colitis therapies**

Note: for all therapies, except for Remicade in patients with acute exacerbations, stop therapy upon failure, or when surgery is needed, or after 12 months of treatment, whichever occurs first. Continue only with evidence of benefit. Consider discontinuing treatment for patients in stable clinical remission. Relapsing patients after treatment holiday may have the option to be retreated.

6-MP = mercaptopurine; AZA = azathioprine; CS = corticosteroid; ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; QALY = quality-adjusted life year; TA = technology assessment; TNF = tumor necrosis factor; UC = ulcerative colitis

Source: NICE, 2008; 2015a/b

ENTYVIO IS RESTRICTED TO THE THIRD LINE IN CD AFTER FAILURE WITH A TNF-ALPHA INHIBITOR, AND REQUIRES A PATIENT ACCESS SCHEME

Despite having a marketing authorization for patients who have failed conventional biologics or TNF-alpha inhibitors, Entyvio is only reimbursed for patients after failure with a TNF-alpha inhibitor, as the drug was not found to be cost effective in the second line. The ICER for the TNF-alpha inhibitor-naïve population demonstrated that biologics dominate Entyvio (ie have better efficacy and lower costs). For patients who have failed TNF-alpha inhibitors, Entyvio is cost effective, with an ICER versus conventional non-biological therapy of £21,600 per QALY gained. Clinical experts advising NICE have indicated that due to a high unmet need for patients who have failed TNF-alpha inhibitor therapy, they envisage that Entyvio will be most useful in patients who have failed at least two TNF-alpha inhibitors, and that, in practice, Entyvio will be used after TNF-alpha inhibitors as physicians have extensive experience with the biologics, indicating that this restriction will have little impact on the product's potential in CD (NICE, 2015c).

Stelara's faster onset of action and a free first dose, coupled with wider NICE recommendations, give the drug an advantage over Entyvio in CD

Stelara's wider NICE recommendation compared with Entyvio provides the drug with an advantage in CD. While NICE restricted Entyvio's use in CD to third line after TNF-alpha inhibitor failure, the committee approved Stelara's use in line with TNF-alpha inhibitors. Clinical experts consulted by NICE agree that Stelara is unlikely to displace TNF-alpha inhibitors despite the approval, as there is considerable clinical experience of using the TNF-alpha inhibitors in real-world settings. Nevertheless, as Entyvio is restricted to patients who have failed therapy with TNF-alpha inhibitors, and Stelara does not have this restriction, the IL-12/23 could potentially push Entyvio further down the therapeutic pathway. Both drugs are subject to the limit of a maximum of 12 months' on-treatment time.

NICE considers Stelara as innovative and cost effective, noting that there is a positive impact of reduced administrative burden during the maintenance phase, which helps to minimize disruption to patients' work and daily life activities. As this is not captured in the economic modeling, the therapy may be more cost effective than originally estimated. The company's cost-minimization analysis using Stelara's confidential pricing demonstrates lower total costs after 12 months compared to other biologic treatments at the list price. NICE, however, acknowledges that prices for biologics could be lower than are listed, and ultimately recommends physicians to take into account the total cost of treatment when making prescribing decisions (NICE, 2017).

Stelara's perceived faster onset of action coupled with the offer of a very low-cost loading dose gives the drug a further edge over Entyvio, as some payers are receptive to the potential for lower costs and quicker identification of non-responders.

"What the companies are marketing is that you can pretty much identify from the IV and this induction dose whether you are going to get responders, whereas vedolizumab takes longer, but I think what my clinician has discussed with me is that patients either respond very well or not at all. There is no kind of that midline in terms of a responder for vedolizumab, so it is quite easy to go: 'yes, leave them on,' or 'no, they are not getting any benefit.' It is when you get that partial response that it is sometimes difficult, whereas we do not see that with vedolizumab, but you are correct it takes longer to see a response, and of course ustekinumab, after the IV which I think they have priced at a pound or something ridiculous, so it costs us nothing to see whether there is a responder or not. Then it is only the subcutaneous ones that we would continue to pay for when the charges become significant."

UK regional payer

ENTYVIO IS REIMBURSED IN THE FULL PATIENT POPULATION FOR UC WITH A PATIENT ACCESS SCHEME AND A ONE-YEAR STOPPING RULE

Entyvio is reimbursed for moderate to severe active UC patients in line with its European Medicines Agency approval, assuming that the manufacturer provides the drug at discount in accordance with its PAS, and that patients switch to conventional therapy after one year of treatment. The committee subdivided the population into patients naïve to TNF-alpha inhibitors and those refractory to the biologic. For patients with prior failure on a TNF-alpha inhibitor, the committee used two ICER values instead of the manufacturer's ICER, which resulted in ICERs of £27,500 (Swinburn et al.) and £31,900 (Woehl et al.) versus conventional therapy. Although these were in the upper limit for cost effectiveness, given uncertainty in the utility values, the cost of surgery and costs post-surgery, and Entyvio's innovative mechanism of targeting gut-system immunity, the committee concluded that the PAS and a start-and-stop algorithm would make the drug cost effective (NICE, 2015b).

For patients naïve to TNF-alpha inhibitors, the manufacturer and working group had highly discrepant ICER calculations. The manufacturer's ICER was £5,000 versus conventional therapy and £7,000 versus Humira per QALY gained, whereas the working group estimated an ICER versus conventional therapy of £53,000 per QALY gained. In the assessment, Humira dominated Entyvio, but the committee posited that a PAS was not considered in the original calculations, which would have lowered the ICER. If the working group had applied utility values from Swinburn et al. instead of Woehl et al., with a one-year stopping rule, Entyvio's ICER was less than £20,000 per QALY gained, and was therefore dominant versus relative comparators. As there was uncertainty surrounding the utility values, costs of surgery, and costs post-surgery, the committee concluded that Entyvio would be cost effective with a PAS and a mechanism to stop treatment after one year (NICE, 2015b).

REMICADE IS REIMBURSED FOR PEDIATRIC UC PATIENTS, AS PER ITS MARKETING AUTHORIZATION, DESPITE FAILING THE COST-EFFECTIVENESS TEST

NICE approved Remicade for adolescent and pediatric patients with severe UC despite cost-effectiveness analyses that were above the £20,000–£30,000 threshold. The committee subdivided the patient population into those who were candidates for colectomy, and those in whom the procedure was not suitable. Colectomy dominated Remicade in patients who were candidates for the procedure, while in those unsuited for colectomy, Remicade versus conventional therapy had an ICER of £68,400 per QALY gained (QALYs: 0.34; cost: £23,268). Although the committee stated that there was a 0% chance for Remicade to be cost effective in either patient population, the drug was still reimbursed in line with its marketing authorization. This was because the working group felt that the analysis had underestimated the cost effectiveness of TNF-alpha inhibitors in this patient population. There was both uncertainty around the cost, which was likely to be overestimated, as well as potentially uncaptured QALY benefits, which when combined would improve the cost effectiveness of TNF-alpha inhibitors (NICE, 2010). Datamonitor Healthcare therefore anticipates that gastroenterologists will face few obstacles in prescribing Remicade for the pediatric population.

XELJANZ'S PRICING WILL LARGELY BE DICTATED BY ITS COST IN RA, WHICH WILL NEED TO BE COMPARABLE TO OLUMIANT

UK payers expect Xeljanz's price in UC to be based on the target price Pfizer will aim for in RA, as the RA indication is more prevalent than UC. Further, as Olumiant has become the first JAK inhibitor to launch in the UK market, ahead of Xeljanz, this will have a large impact on the latter drug's price. To remain competitive, Pfizer must be ready to concede to discounts, as Olumiant was launched at a lower price than TNF-alpha biosimilars, which will remain competitive with future biosimilar launches, much to the surprise of UK payers. At a premium, Xeljanz will be pushed to later in the treatment paradigm. UK payers state that even if Xeljanz and the JAK inhibitors play a more significant role in the gastroenterology indications due to fewer therapeutic options, their price will ultimately count in terms of their placement in the treatment paradigm.

"It is going to be down to price whether we decide – and because it is going to be competing with baricitinib in RA, I think it will have to have a very close comparative price otherwise it will not get used at all, because we will go with baricitinib rather than tofacitinib. So, I think Lilly have kind of paved the way a little bit in terms of price expectations, but if it is priced appropriately we would use it in TNF-naïve patients, because

the data is superior, and it is oral, and it may be more cost effective.

I know what the price [of Olumiant is], and it has been absolutely amazing for the UK market. I cannot believe how they have done it, [...] it is going to be cheaper than any of the adalimumabs will be likely come out at initially because it is cheaper than biosimilar infliximab already, which we have got massive discounts on.

[If Xeljanz is priced higher,] we will use baricitinib, and then because we will have tofacitinib in UC and maybe not baricitinib at that point, we would assess it in this indication, but it is still going to be more expensive than the existing biologic, so we would probably use it after biosimilars rather than alongside, which is a possibility in RA. [...] I hate to say it, because I do not like it when people say it, but actually this decision is going to be very, very price-sensitive. [...] As we have already seen with the biologics, the influence of RA, the experience of RA, but sometimes it becomes more important because they have got less options in gastro. So, from a clinical point of view, the drugs become more interesting, and we need to be clear about what we are doing because there are not as many options, whereas in RA they have got lots and lots of choices."

UK regional payer

MANAGING SPEND FOR IBD DRUGS WILL REVOLVE AROUND START-AND-STOP CRITERIA

UK payers state that a large part of managing the use of IBD drugs will involve start-and-stop criteria used to determine if treatment should continue, or if patients need to weaned off their treatment. UK payers state that as soon as patients achieve remission, the focus is to decrease therapy such that the patient can be removed entirely from the regimen. This is contrary to other regimens, where patients are on the same treatment for life. Payers report that UC and CD patients have a high barrier to overcome before they are put on these expensive therapies, and payers are eager to stop treatments when patients are in remission.

"It has all been about start criteria and stop criteria. Who gets it and how long do they have it for? [It is] a bit like rheumatoid [arthritis], they need to fail the other standard treatments that exist: steroids, azathioprine, immunosuppressants. [...] Once they have started treatment, if the biologic succeeds, the payer will try and withdraw it. If the biologic fails, the payer will try and withdraw it. So, the payer seems quite keen on just getting them off the biologic for whatever reason they have started. If you have a blood pressure treatment, the eligibility is quite low to start and you just keep treating, right? You do not ever stop. If you look at biologics in UC, you need quite a high hurdle and threshold to access a biologic; you need to have failed current first-, second-, third-line therapies, and once you access a biologic, if the drug does not work you stop it. If the drug puts you into remission and is successful, you have to try and stop it. If the drug gives you adverse events, you have to stop it. If the patient does not respond, you have to stop it. So everything is leading to taking them off."

UK local payer

REGIONAL FORMULARY DECISIONS

In the UK, decisions regarding regional formulary inclusions and exclusions are mostly dictated through NICE's multiple and individual TAs. As these documents mandate the availability of drugs within the NHS, all medications reviewed and recommended via TAs are expected to be in regional formularies. Conversely, medications rejected by NICE are also expected to be excluded. Datamonitor Healthcare surveyed five formularies, which were chosen based on a combination of factors including largest impact and patient population size, in order to understand the formulary decisions behind key IBD drugs. Please refer to the datapack to see inclusion/exclusion from formularies, traffic light status, and indications of first choice versus alternative therapies for Birmingham CrossCity; Bristol, North Somerset and Gloucestershire Health Community; Dorset NHS; Greater Manchester Medicines Management Group; and South East London Joint Medicines CCGs.

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METHODOLOGY

PRIMARY RESEARCH

Datamonitor Healthcare conducted primary research consisting of in-depth one-hour telephone interviews with the following payers:

- **US (2)** – Two payers (medical or pharmacy directors of regional health plans)
- **France (1)** – A former Transparency Committee member
- **Germany (2)** – A sickness fund member, and a physician association payer
- **Italy (1)** – A former member of the Italian Medicines Agency
- **Spain (2)** – Two local/regional payers
- **UK (2)** – One clinical commissioning group formulary pharmacist, and one hospital formulary pharmacist.

PRICE ASSUMPTIONS

Datamonitor Healthcare uses national formularies to gather pricing information per product. As the prices presented in formularies can differ, showing prices at different stages in the supply chain, Datamonitor Healthcare uses backing-out formulas to adjust formulary prices in order to obtain estimates of ex-factory wholesale prices. The tables below outline the sources and calculations used in the US and five major EU markets (France, Germany, Italy, Spain, and the UK).

For Japan, prices are taken from the National Health Insurance drug database. These prices are the retail price exclusive of consumption tax, and therefore it is important to note that the sales given for Japan may be inflated compared to other countries, depending on the extent of price markups at different stages in the supply chain. However, Datamonitor Healthcare has validated its patient-based sales estimates with company-reported sales in Japan where available, and believes the impact to be minimal.

Figure 1: **Price sources and calculations for the US and EU, by country**

Country	Starting source	Formulary price	Net retail price formula	Ex-factory pharmacy price formula	Ex-factory wholesale price formula	Source for formulas	Note
US	Red Book	AWP	n/a	n/a	WP = AWP/1.2	Red Book (2017)	Assumes AWP is 120% of WP
France	Le Dictionnaire Vidal	Retail price inclusive of VAT	RPN = RP/1.021[a]	PP = RPN/[b]	WP = RPN/1.0668[c]	Eco-Santé France (2012) Le Pharmacien (2017) Patented Medicine Prices Review Board (2017)	[a]Assumes 2.1% VAT for reimbursed products and 5.0% VAT for non-reimbursed products [b]PP calculation accounts for 0% pharmacy margin for first €1.91 of WP, 25.5% margin for WP between €1.92 and €22.90, 8.5% margin for WP between €22.91 and €150, 6% margin for WP between €150.01 and €1,500, and 0% margin for WP ≥€1,500.01 Also assumes a fixed dispensing fee of €1.00 [c]Assumes a wholesale margin of 6.68%, with a minimum value of €0.30 and maximum value of €30.06
Germany	Lauer-Taxe	Retail price inclusive of VAT	RPN = RP/1.19	PP = (RPN - 8.51)/1.03	WP = (PP - 0.70)/1.0315	German Ministry of Health (2017)	
Italy	L'Informatore Farmaceutico	Retail price inclusive of VAT	RPN = RP/1.10	n/a	WP = 0.6665 x RPN	Patented Medicine Prices Review Board (2017)	
Spain	Catalogo de Medicamentos	Retail price inclusive of VAT				PHIS (2010)	Assumes hospital drugs are procured at ex-factory prices
		If 0<RP≤131.15	RPN = RP/1.04	PP = RPN/1.279	WP = PP/1.076		
		If 131.16<RP≤255.75	RPN = RP/1.04	PP = RPN - 7.54	WP = PP – 38.37		
		If 255.76<RP≤573.05	RPN = RP/1.04	PP = RPN - 7.54	WP = PP – 43.47		
		If RP>573.06	RPN = RP/1.04	PP = RPN - 7.54	WP = PP – 48.37		
UK	British National Formulary	Ex-factory pharmacy price	n/a	n/a	WP = 0.875 x PP	Patented Medicine Prices Review Board (2017)	Assumes similar pricing presented in MIMS and BNF

AWP = average wholesale price; BNF = British National Formulary; MIMS = Monthly Index of Medical Specialities; PP = pharmacy price; RP = retail price inclusive of VAT; RPN = net retail price; WP = wholesale price

Source: various (see above)

EXCHANGE RATES

Using the calculated ex-factory wholesale price, the price per mg or mcg is calculated. This is multiplied by Datamonitor Healthcare's annual dosing assumptions in order to obtain an annual price per patient.

Table 36: **Exchange rates used for calculating drug prices**

Currency	Local currency to USD
EUR	1.1067
GBP	1.3552
JPY	0.0092

Source: Open Exchange Rates, 2017

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