COMPARISON OF EU5 MARKET ACCESS DECISIONS FOR CROHN'S DISEASE BASED ON THE PRISMACCESS® DATABASE

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INTRODUCTION:

- Crohn's disease (CD) is a long term condition in which inflammation of the digestive system leads to diarrhoea, abdominal pain, tiredness and weight loss. There is no cure for CD at the moment [1].
- When the CD is active, drug treatment is usually used to manage the symptoms quickly and bring on remission.
- Prevalence of CD for Germany in 2010 was 322 (95% confidence interval [CI]: 302-346) per 100000. In line with worldwide reports, the numbers suggest a considerable increase for CD prevalence in Germany since the 1980s, which need to be adapted by healthcare services and dealt with the burden associated with increasing numbers of patients. [2]
- New therapies have been launched in Europe over the last few years. One key question remains if these new therapies reach patients in terms of market access in various European countries and how the national HTA agencies have decided on these therapies.
- This study visualizes the heterogenous multiple decisions by EU-5 HTA agencies using the Prismaccess®/Evalumade® database and their three-colored scale. Hence, this study will shed light on those decisions in a transparent and understandable manner for industry.

METHODS:

- The international HTA database Prismaccess® includes over 20.000 decisions by market access authorities worldwide.
- This study includes the decisions of the following authorities (countries):
  - o France – Transparency Committee Haute Autorité de Santé – TC HAS / CEESP
  - o England – National Institute for Health and Care Excellence - NICE
  - o Scotland – Scottish Medicines Consortium - SMC
  - o Germany – Federal Joint Committee - G-BA
  - o Italy – Decisions on regional level of the Regions Emilia-Romagna & Veneto. Additionally, on a national level decisions of Italians Medicines Agency – AIFA were considered.
  - o Spain – Agencia Española de Medicamentos y Productos Sanitarios – AEMPS. Additionally, decisions on the level of the Hospital Network (GENESIS) and also regional decisions of Andalucia, Aragon, Basque, Catalonia (CAMHDA) were considered.
- All decisions on therapeutic areas labeled for CD launched between January 1st 2011 until October 1st 2018 were considered for a systematic analysis.
- Results are labeled according to the national rating. Table 1 explains the national reimbursement grading systems and additionally an overall comparable rating system, visualizing all decisions using a traffic light system. While green and red are self-explaining, yellow means a restriction from a clinical, but also from an economic point of view. As example for France and Germany, if there is an added benefit granted for the therapy in total, but at least in one subgroup, a "no proven added benefit" was granted, then the restriction is assumed ("yellow").
  - o Green – Recommended without limitation
  - o Yellow – Recommended with limitation
  - o Red – Not recommended

Table 1: National grading systems and overall grading system in the Prismaccess®/ Evalumade® database

Overall rating system	France TC HAS – ASMR	Germany G–BA – Added benefit	Spain AEMS ITS – Cost–Effect.	England NICE – Cost–Effect.	Scotland SMC – Cost–Effect.	ITALY – Added benefit
Recommended without limitations	ASMR IV and higher in all subgroups	Added benefit in all subgroups	Recommended	Accepted	Accepted	Accepted
Recommended with limitations	ASMR V / Insufficient in at least one subgroup	No added benefit in at least one subgroup	Recommended with restrictions	Accepted with limitations	Restricted	Accepted with limitations
Not recommended/ not reimbursed	Insufficient	Lesser benefit	Not recommended	Not recommended	Not recommended	Not recommended

RESULTS:

- A total of 50 decisions have been considered for the five countries since January 2011 until October 2018 for 10 different drugs. Figure 1 shows the development over time as also the different numbers per country. The assessed drugs were biologicals as Adalimumab, Infliximab, Ustekinumab and Vedolizumab, as also non-biologicals.
- The most decisions are identified for the French HAS (28 assessments), The high number is explained re-assessment e.g. due to new data. In detail were Adalimumab (6 decisions), Infliximab (5), Ustekinumab (2) and Vedolizumab (2) were assessed, and also non biologicals such as Budensonide (6), Mesalizine (3), Hydrocortisone (2), Methotrexate (1), Sufaslazine (1). Figure 2 shows that a substantial medical benefit (SMR) is given at most of the subgroups. An added benefit (ASMR of IV and higher) is hardly given, as shown in figure 3.
- Additionally, in France 2 cost-effectiveness decisions from the CEESP, for Vedolizumab and upcoming new drug Darvadstrocel (ALOFISEL) are published.
- For Scotland, 9 decisions were identified by the SMC. As in France, multiple decisions for one drug are leading to a higher number. In detail, Adalimumab (3), Infliximab (3), Budesonide as also Ustekinumab and Vedolizumab were assessed.
- For the other countries such as England, Germany and Spain, only decisions for Ustekinumab and Vedolizumab could be identified. In detail for Germany – G-BA 1 (Vedolizumab), Englands NICE 2 (Ustekinumab, Vedolizumab), and Spain 5 on national level (AEMPS IPT) (Vedolizumab (4), Ustekinumab).
- Additionally, in Italy at a national level, 3 decisions of AIFA could be identified (Ustekinumab, Adalimumab (2)). Reimbursement decisions on a regional level could not be identified.
- Due to the smaller number of available decisions in Germany, England, Italy and Spain, the focus of this research is on the two biologicals Ustekinumab and Vedolizumab. A comprehensive analysis of this data is presented in Table 2 for Ustekinumab (STELARA) and in table 3 for Vedolizumab (ENTYVIO).
- For Vedolizumab (ENTIVYO), results of the agencies of Spain (4), England, Scotland, Germany and France (3) are available. All agencies criticized the clinical trial data respective to the comparator Placebo and the small effect sizes. The decisions differ by patient population and recommended use and range from a use as mentioned in the MA label (Spain/ Catalonia) to the restriction in third line use (France) (see Table 3).
- For Ustekinumab (STELARA), (see Table 2), results of the agencies of Spain, Italy, England, Scotland and France are available. All agencies criticized the clinical trial data respective to the comparator Placebo, which is not considered to be the appropriate in light of the current management strategy, particularly as Adalimumab and Infliximab are available. The decisions differ in the patient population, where Ustekinumab in CD should be used.
- What is coming next? Currently decisions for Darvadstrocel (ALOFISEL) in France, Germany, England, Scotland and Spain are prepared and expected for the first half of 2019. ALOFISEL is the first stem cell therapy to treat complex perianal fistulas, which is one of the most disabling complications of Crohn's disease.

Figure 1: CD descisions by the chosen agencies sorted by year 2011 – 2018, extracted from Evalumade®

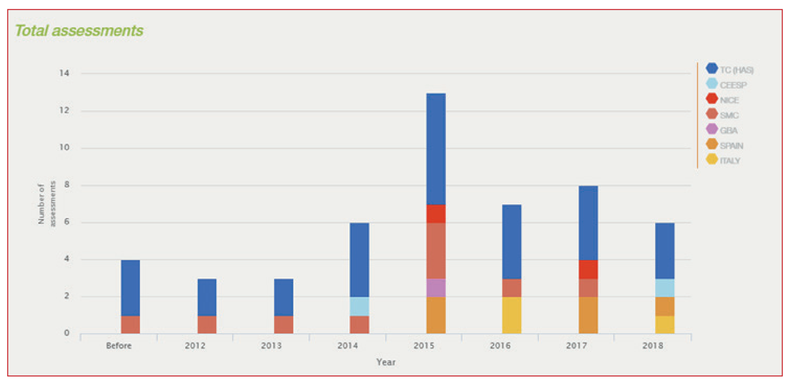

Figure 2: SMR shown for CD drug subgroups 2011–2018 in France, created by Evalumade®

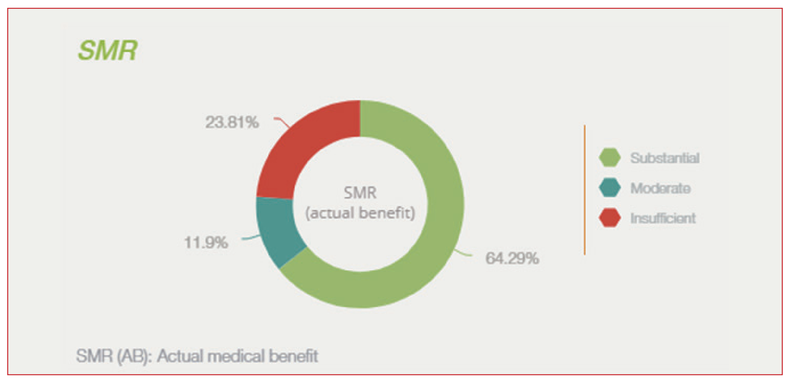

Figure 3: ASMR shown for CD drug subgroups 2011–2018 in France, created by Evalumade®

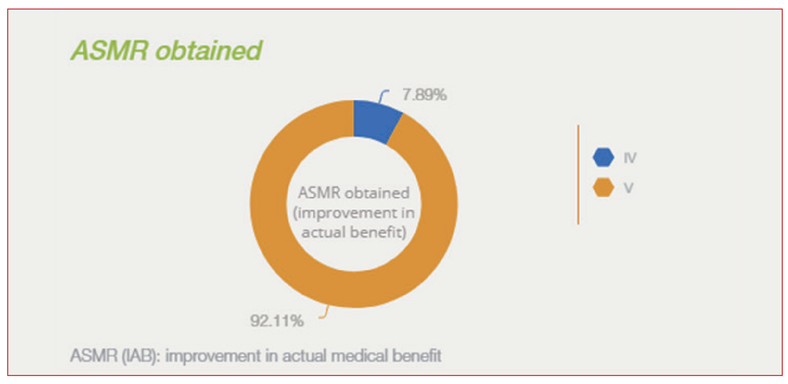

Table 2: Results for Ustekinumab (STELARA) in the Prismaccess®/Evalumade® database

Indication approved by EMA: Indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Date of decision	Results	ACT	Patient population	Additional Information
ENGLAND 12/07/2017 NICE TA STA456	Accepted	Placebo	Moderately to severely active Crohn's disease for adults who were previously treated with either conventional therapy or a TNF-alpha inhibitor.	• Stelara is recommended for treating moderately to severely active Crohn's disease for adults who were previously treated with either conventional therapy or a TNF-alpha inhibitor. • The results of the clinical trial with placebo was accepted. • In clinical trials, the medication demonstrated higher rates of response and clinical remission in comparison to placebo. • Stelara is associated with lower costs in year 1 than comparator treatments (Infliximab, Adalimumab, Vedolizumab, Conventional Non-Biological Care) and is therefore a cost-effective option for use within the NHS. • Clinical trials: o UNITI-1 o UNITI-2
Scotland 10/07/2017 SMC Full submission 1250/17	Accepted	Placebo	Patients with moderately to severe Crohn's disease who have failed on or are not able to tolerate TNFα antagonists or immunosuppressants or corticosteroids.	• Stelara offers an alternative treatment for patients with moderately to severe Crohn's disease who have failed on or are not able to tolerate TNFα antagonists or immunosuppressants or corticosteroids. • Patient Access Scheme (PAS) has to be granted. • The results of the clinical trial with placebo was accepted. • In comparison to placebo, Stelara improved clinical response and remission in both the induction and maintenance clinical studies. • The use of Stelara is a cost-effective treatment in relation to its comparators (Adalinumab, Infliximab, Vedolizumab). • Clinical trials: o UNITI-1 o UNITI-2
France 08/03/2017 TC STELARA 45mg	Substantial ASMR IV	Infliximab Adalinumab Vedolizumab	Crohn Disease, as a 3rd line treatment in patient who have had an inadequate response to conventional therapy (corticosteroids or immunosuppressants) and at least one TNF-antagonist	• Not recommended in naïve anti-TNF patients • STELARA 45 mg and 90 mg solution for injection o Medicine for initial hospital prescription. o Prescription restricted to specialists in dermatology, rheumatology, internal medicine or gastroenterology and hepatology. o Exception drug status • The Committee considers that STELARA provides a minor improvement in actual benefit (IAB IV) in the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies. • It should be restricted to patients who have failed a conventional therapy (corticosteroids or immunosuppressants) and at least one TNF inhibitor, taking into consideration its demonstrated efficacy and the identified medical need in this population. • In patients who are naive to TNF inhibitors, its role in relation to TNF inhibitors cannot be determined because there was no direct comparison between ustekinumab and this class of medicines, although this was feasible. • A new presentation in the form of 130 mg concentrate for solution for intravenous infusion is available only for induction treatment of CD. • Clinical trials: o UNITI-1 o UNITI-2 o IM-UNITI
	Insufficient		Crohn Disease in patient who have had an inadequate response to conventional therapy (corticosteroids or immunosuppressants) and naïve anti-TNF patients	
France 08/03/2017 TC STELARA 130 mg	Substantial ASMR IV	Infliximab Adalinumab Vedolizumab	Crohn Disease in patient who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy and at least TNFα antagonist or have medical contraindications to such therapies	• Not recommended in naïve anti-TNF patients • Medicinal product reserved for hospital use • Prescription restricted to specialists in gastroenterology, hepatology or internal medicine. • The comparison with mere placebo is regrettable in light of the current management strategy, particularly as adalimumab and infliximab had marketing authorisation when these studies were conducted. A comparison with a TNF inhibitor is needed for the role of ustekinumab to be determined in relation to these medicines. • No specific safety signals were detected from analysis of the available safety data, with respect to the main risks already identified since STELARA was marketed in other indications. • Likely to have an budget impact. • Clinical trials: o UNITI-1 o UNITI-2 o IM-UNITI
	Insufficient		Crohn Disease in naïve anti-TNF patients	
Germany G – BA	No decision available			
Spain 10/8/2017 (AEMPS) IPT Additional range	Reimbursed	Placebo	Indicated for the treatment of moderate to severe active Crohn's disease in adult patients who have had an inadequate response, have a loss of response or are intolerant of conventional treatment or TNFα antagonists or have medical contraindications to those treatments .	The Dirección General de Cartera Básica de Servicios del Sistema Nacional de Salud y Farmacia has funded ustekinumab treatment in Crohn's disease in those adult patients with moderate to severe active disease who have had an inadequate response, have a loss of response or intolerant to conventional treatment and TNF-alpha antagonists, or as an alternative to TNF-alpha antagonists when they present medical contraindications to these treatments. In these situations, the choice of ustekinumab or its alternatives will be based on efficiency criteria. Ustekinumab has been shown to be statistically superior to placebo in inducing clinical response after six weeks of treatment in both naïve anti-TNF patients and in those with anti-TNF failure or intolerance. During the maintenance phase, all patients started in clinical response, there was a significant difference in the number of patients in clinical remission at week 44 compared to placebo, although there was a loss of response during the maintenance phase And the results in the population with anti-TNF failure do not reach statistical significance. Although direct comparisons are not available, according to the data presented above, it does not offer anti-NTF efficacy advantages, representing a clinical alternative in both naïve and anti-TNF patients, as well as in patients with failure or intolerance to them, providing a faster onset of action than vedolizumab. Most of the adverse effects are known for the active ingredient in the above authorized indications. Those identified in the clinical development of this new indication are considered clinically manageable. The potential risk of deep venous thrombosis has been included in the risk management plan. • Clinical trials: o UNITI-1 o UNITI-2 o IM-UNITI
ITALY 09/08/2018 AIFA (National)	Addition to the SSN	Not available	Indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies	Validity of the contract: twenty-four months. Compulsory discount, applied on the ex-factory price, to be applied to the public structures of the National Health Service, including private accredited health facilities as negotiated conditions.

Table 3: Results for Vedolizumab (ENTYVIO) in the Prismaccess®/Evalumade® database

Indication approved by EMA: Entyvio is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Date of decision	Results	ACT	Patient population	Additional Information
England August 2015 NICE STA TA352	Accepted	Placebo Economic compatator: Conventional non-biological therapy	Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy	• Limitation: If a tumour necrosis factor-alpha inhibitor has failed or cannot be tolerated or is contraindicated • Limitation: If the company provides it with the discount agreed in the PAS • Vedolizumab is a cost-effective treatment for people for whom TNF alpha treatment has failed compared to conventional non-biological therapy. Cost-utility analysis: against Conventional non-biological therapy 21620 GBP. • Incorporating the updated PAS • Vedolizumab improved clinical remission rates compared with placebo but the long-term effects of the drug were uncertain. • Clinical trials: o GEMINI II o GEMINI III
Scotland 13/07/2015 SMC Full submission 1064/15	Restricted Use	Placebo Economic compatator: Conventional therapy	Moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a tumour necrosis factor-alpha (TNFα) antagonist.	• Patients who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. For people in complete remission at 12 months, prescribers should consider stopping vedolizumab, resuming treatment if there is a relapse. • Study showed that more patients treated with vedolizumab achieved clinical remission at week 6 compared with placebo. • Economic analysis compared vedolizumab with conventional therapy. There were some uncertainties and weaknesses with the analysis but overall it was found that vedolizumab could offer value for money for the treatment of this patient group. Cost-utility analysis: ICUR 6922 GBP. ICER with PAS. • This SMC advice is dependent upon the continuing availability of the PAS or a list price that is equivalent or lower. • Clinical trials: o GEMINI II o GEMINI III
France 07/01/2015 TC	Moderate ASMR V	Adalimumab, Infliximab Failed anti-TNF treatment: none with MA	Crohn's Disease: in patients in failure (inadequate response, lost response, intolerance) of corticosteroids, immunosuppressants and anti-TNF (after failure of the actual therapeutic strategies)	• Only for patients who failed with corticosteroids, immunosuppressants and anti-TNF in Crohn disease • Clinical trials: o GEMINI I o GEMINI II o GEMINI III • For Crohn's disease: no drug alternatives available, but, modest and questionable clinical benefit • In naive anti-TNF patients: No comparative study versus anti-TNF and superiority of available therapeutic alternatives.
	Insufficient NO ASMR		Crohn's Disease: in patients naïve of anti-TNF treatment (after failure of the actual therapeutic strategies)	
France 06/12/2017 TC ENTIVYO 300 mg Reassessment Hospital use (COLL)	Substantial	Adalinumab, Infliximab, Ustekinumab	Crohn's disease: patients who have failed conventional therapy and at least one anti-TNF or who have contraindications to these treatments (3rd line)	• ENTYVIO has a third-line role in the management of Crohn's disease, after failure of a conventional therapy including an immunosuppressant (such as azathioprine or 6-mercaptopurine) or a corticosteroid and at least one anti-TNF (adalimumab or infliximab). • The delay in action of ENTYVIO, during which patients remain exposed to the complications from Crohn's disease, should be taken into account. • The Committee wishes to receive the results of the studies in progress or planned indicated in the opinion • The re-assessment of the clinical added value of ENTYVIO in the population limited to only patients with CD who have failed at least one anti-TNF (third-line) is essentially supported by 1) the additional analysis (low level of evidence) of GEMINI III and GEMINI II, 2) approximately 5-year follow-up data from the extension 3) data from the temporary authorisation for use by a cohort [ATU cohorte in French] and its extension • Clinical trials: o GEMINI II and III data combined o GEMINI II and III extension o ATU cohort safety data France
	Insufficient		Crohn's disease: in anti-TNF-naive patients	
France 25/11/2014 CEESP	Acceptable (substantial methodological reservation)	Conventional therapy	Indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a tumour necrosis factor-alpha (TNFα) antagonist.	• Cost utility analysis • ICUR: 53806 €/QALY gained. • Efficiency has not been established versus active treatment in patients who failed at least one anti-TNF in the absence of sufficient data to other anti-TNF, while in practice, patients are referred to another anti-TNFa or have dose increases. If Vedolizumab was compared with active treatment, the difference between the claimed price and that of antiTNFα already on the market would lead to a different ICER of Vedolizumab. • Clinical trials: • GEMINI II • GEMINI III
Germany 08/01/2018 G–BA	No added benefit proven	A TNF alpha antagonist (adalimumab or infliximab)	Patients with moderate to severe active Crohn's disease who have responded inadequately to conventional therapy, no longer respond to it or have an intolerance to an appropriate treatment	• The manufacturer presented neither a direct nor an indirect comparison with the ACT Adalinumab or Infliximab. Therefore an added benefit is not proven.
Germany 08/01/2018 G–BA	No added benefit proven	TNF-alpha antagonist (infliximab or adalimumab in consideration of prior therapies)	Patients with moderate to severe active Crohn's disease who have not Responded to any of the tumor necrosis factor-alpha (TNF) antagonists insufficient, no longer respond to it or to have intolerance to an appropriate treatment	• The manufacturer presented the two RCT trials against Placebo. This is neither the ACT nor it is suitable to proof efficacy or safety profile. The shown effect sizes of Vedolizumab are very small and there is no proof against a lesser benefit. Therefore an added benefit is not proven. • Clinical trials: o GEMINI II [C13007] o GEMINI III [C13011]
Spain 10/06/2015 (AEMPS) IPT	Recommended	Placebo	Moderate to severe active Crohn's disease in those patients who have failed treatment with conventional therapy and anti-TNFα drugs or as an alternative to anti-TNFα - TNFα when there is contraindication	• In Crohn's disease, vedolizumab is not an alternative because the data suggest a modest effect on efficacy and a delay in induction of remission compared to other biological agents. However, due to the scarce therapeutic alternatives in patients with anti - TNFα failure or intolerance, vedolizumab could represent a treatment option in these patients. • Clinical trials: o GEMINI II [C13007] o GEMINI III [C13011]
SPAIN 16/03/2015 GENESIS National hospital network	D - List with restrictions	Placebo Economic compatator Adalimumab Infliximab	Moderate to severe Crohn's disease Prescription and dispensing conditions: As 2nd or 3rd line treatment	• VDZ is the most expensive alternative compared to Adalimumab and Infliximab. • As second line: economic impact after failure to 1 anti-TNF according to the% failure of GEMINI II and III, the impact would be 31 mill. to 41 mill. €/year • In third line: economic impact after failure to 2 anti-TNF, 31 mill. to 62 mill. €/year. • Clinical trials: o ADA (Classic I) o VDZ (GEMINI II) o VDZ (GEMINI III) o IFZ (Targan et al)
SPAIN 24/04/2018 (AEMPS) IPT	Recommended	Placebo	Vedolizumab has been funded in the treatment of moderate to severe active Crohn's disease in those patients who have failed treatment with conventional therapy and anti-TNFα drugs or as an alternative to anti-TNFα - TNFα when there is contraindication	• Additional data presented, but no change in the opinion. • To position the drug in therapy it is necessary to put the trial data in the context of the available therapeutic alternatives. Despite the lack of data on direct comparisons, and the existence of differences in the design of the studies among the therapeutic alternatives, the similarities between the studies in CD for the different monoclonal antibodies in terms of the population included (in all cases) moderate to severe Crohn's disease) and in the definition of the measurement of the CDAI efficacy variable <150 (primary variable in adalimumab and vedolizumab and secondary in infliximab), lead us to consider that, in general, the effect of vedolizumab is modest compared to the alternatives available in Crohn's disease. • In February 2018, a modification of the financing conditions was resolved, extending them to the entire therapeutic indication included in its technical file. These final considerations do not modify the clinical positioning, so it is not considered necessary to modify the previous conclusions. • Clinical trials: o GEMINI II [C13007] o GEMINI III [C13011]
SPAIN 04/09/2017 CAMHDA Catalonia	Recommended with limitation	Adalimumab Infliximab Ustekinumab	Treatment of active, moderately to severe Crohn's disease in adult patients who have had an inadequate response, have a loss of response or are intolerant to conventional treatment or with an alpha tumor necrosis factor (TNFα) antagonist.	The Pharmacotherapeutic Harmonization Program recommends the use of adalimumab, infliximab, ustekinumab and vedolizumab for the treatment of Crohn's disease in adult patients in the field of CatSalut: • The indication, follow-up and evaluation of the therapeutic response by health professionals be carried out in accordance with the clinical criteria annexed to this opinion. • The field of prescription of biological drugs be carried out in hospitals with experience in the diagnosis and treatment of patients with inflammatory bowel disease and that ensure adequate comprehensive health care for affected patients. • Follow up people who are treated with this drug. The medical personnel responsible for the treatment must provide the clinical data to CatSalut, so that the effectiveness, safety and adaptation to the treatment can be verified, through the registration of patients and MHDA treatments. • Anti-TNFs have a known safety profile and no significant differences have been observed between them. Infections are one of the most frequent adverse effects. • Vedolizumab has been associated with cases of nasopharyngitis, but due to its mechanism of action, it presents less risk of systemic immunosuppression than anti-TNF and ustekinumab. • Clinical trials considered: CLASSIC Y, GAIN , CLASSIC II, CHARM, EXTEND, Targan et al. 1997, ACCENT-I, UNITI-I, UNITI-II, IM-UNITI, GEMINI II and GEMINI III

CONCLUSIONS:

- Evidence requirements substantially differ by HTA agency of EU-5 countries and this needs to be considered by industry for both their local HTA submissions and global lifecycle planning processes. Knowledge of this heterogeneity is pivotal for industry to reach their target price across EU-5 countries.
- As shown with the examples of Vedolizumab and Ustekinumab, decision for reimbursement differ in the range of added benefit and also in terms of the patient population, in which the drug is reimbursed or not reimbursed. Also differences can be seen for the appropriate comparator therapies, especially for the use of placebo which is accepted in some countries.
- The authors advocate that one centralized HTA process does not make sense due to several and multiple singularities of each market such as the definition of standard of care. [3]
- The visualization of the heterogenous multiple decisions by EU-5 HTA agencies using the Prismaccess®/Evalumade®database and their three-colored scale makes this hetereogenity more transparent and understandable for industry.

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