HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

16 SEPTEMBER 2020

The legally binding text is the original French opinion version

vedolizumab

ENTYVIO 108 mg solution for injection in pre-filled syringe and in pre-filled pen

First assessment

Key points

Favourable opinion for reimbursement in the following indications:

- treatment of adult patients with moderately to severely active ulcerative colitis 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 (second and third-line treatment);
- 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 conventional therapy and at least one tumour necrosis factor-alpha (TNFα) antagonist (third-line treatment).

Unfavourable opinion for reimbursement in the treatment of TNFα antagonist-naive adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy (second-line treatment).

What therapeutic improvement?

No clinical added value compared to intravenous vedolizumab (ENTYVIO 300 mg).

◗ Role in the care pathway?

Treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis or Crohn's disease.

Subcutaneous ENTYVIO 108 mg (vedolizumab) is intended to be a maintenance treatment. Patients should be given induction therapy with two IV injections of ENTYVIO 300 mg (vedolizumab) by infusion before starting maintenance treatment (see details in the SPC).

◗ ***Ulcerative colitis (UC):***

The objectives of medicinal treatment are first to induce remission and then to maintain corticosteroid-free remission and improve quality of life. The choice of treatment is governed, in particular, by the severity of the disease and the extent of colon damage.

As second-line treatment of moderately to severely active ulcerative colitis in adults who have had an inadequate response with conventional therapy (aminosalicylates, corticosteroids and immunosuppressants), or in whom this treatment is contraindicated or poorly tolerated, TNFα antagonists (infliximab, adalimumab and golimumab) are the reference treatment. Vedolizumab (α4β7 integrin antagonist) may also be prescribed.

However, a TNFα antagonist should be preferred to vedolizumab in two specific clinical situations:
- in the event of extra-intestinal manifestations (rheumatic, cutaneous and ocular manifestations, in particular), given the local action mechanism of vedolizumab;
- with infliximab being the recommended biologic therapy in the event of severe acute colitis (expert opinion).

As third-line treatment, following the failure of conventional therapies and a TNFα antagonist, there are currently three alternatives: vedolizumab, tofacitinib (anti-JAK 1 and JAK 2) and ustekinumab. In the event of no response or loss of response to a TNFα antagonist, it is possible to increase the doses or the administration frequency of the TNFα antagonist or use another TNFα antagonist before considering treatment with vedolizumab or tofacitinib.

It should be noted that, according to the ANSM's new guidelines issued in February 2020, XELJANZ (tofacitinib) should be used with caution in patients with known risk factors for thrombosis, regardless of the indication and dosage. Similarly, the use of tofacitinib at a dosage of 10 mg twice daily for the maintenance treatment of ulcerative colitis in patients with risk factors for thrombosis is not recommended, unless there is no alternative[1].

Role of the medicinal product in the care pathway

The proprietary medicinal product ENTYVIO 108 mg (vedolizumab) administered subcutaneously is an alternative to the IV form of vedolizumab already available. Its role in the care pathway for the treatment of ulcerative colitis is identical to that of the IV form, as second or third-line treatment for patients with moderately to severely active ulcerative colitis with previous failure (inadequate response, loss of response, contraindication or intolerance) to conventional therapy or a TNFα antagonist.

However, a TNFα antagonist should be preferred to vedolizumab in two specific clinical situations:
- in the event of extra-intestinal manifestations (rheumatic, cutaneous and ocular manifestations, in particular), given the local action mechanism of vedolizumab;
- infliximab being the recommended biologic therapy in the event of severe acute colitis (expert opinion).

[1] ANSM: Xeljanz (tofacitinib): new use guidelines in patients at high risk of thrombosis - Letter to healthcare professionals 06/02/2020

Crohn's disease (CD):

The objective of treatment for Crohn's disease is to obtain clinical remission. There is no curative medical treatment for Crohn's disease, but current treatments increasingly often have a suspensive effect, obtaining lasting control of the disease and a satisfactory quality of life.
Management involves aminosalicylates, such as mesalazine or sulfasalazine, corticosteroids and immunosuppressants, including azathioprine, 6-mercaptopurine and methotrexate-MTX. The use of a TNFα antagonist with an MA in moderate to severe forms of Crohn's disease (infliximab and adalimumab) is reserved for patients who have not responded to or are intolerant to corticosteroids and immunosuppressants.

In some patients, an absent or inadequate initial response, a loss of response (tachyphylaxis) or intolerance to treatment with TNFα antagonists may be observed. Depending on the nature of the failure, various therapeutic approaches to optimise treatment may be implemented, such as:
- increasing the doses or administration frequency of TNFα antagonists or adding immunosuppressants,
- switching to a second TNFα antagonist,
- or reintroducing the first TNFα antagonist administered in the event of failure of a second TNFα antagonist.
- use of a biologic therapy with a different target to the TNFα antagonist.

Vedolizumab (ENTYVIO), a monoclonal antibody that targets human α4β7 integrin) and ustekinumab (monoclonal antibody inhibiting interleukins IL-12 and IL-23) has an MA in Crohn's disease and has been given a favourable opinion by the Committee for its management as a third-line treatment only (failure of conventional therapies and a TNFα antagonist).

Surgery may be required as a last resort in some patients but does not cure the condition.

Role of the medicinal product in the care pathway
The proprietary medicinal product ENTYVIO 108 mg (vedolizumab) administered subcutaneously is an alternative to the IV form of vedolizumab already available. Its role in the care pathway for Crohn's disease is identical to that for the IV form. It should be reserved for use as third-line treatment only, i.e., for patients with previous failure (inadequate response, loss of response, contraindication or intolerance) to conventional therapy and at least one TNFα antagonist. In TNFα antagonist-naive patients (second-line treatment following previous failure of conventional treatments), in the absence of a comparison with a TNFα antagonist, the role of this medicinal product compared to TNFα antagonists cannot be specified.

◗ Special recommendations

Given the risk of hypersensitivity reactions with vedolizumab as well as with other disease-modifying biologic therapies (see paragraph 4.4 of the SPC), the Transparency Committee recommends that the first subcutaneous injection of this drug be performed in an appropriate care structure.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

Ulcerative colitis

◗ Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that results in severe chronic bloody diarrhoea, progressing in flare-ups. It leads to a marked deterioration in quality of life and exposes patients to serious complications: acute colitis, dysplasia and colon cancer.

◗ The proprietary medicinal product ENTYVIO 108 mg (vedolizumab) administered subcutaneously is a symptomatic treatment for ulcerative colitis.

◗ The efficacy/adverse effects ratio of vedolizumab is high.

◗ The proprietary medicinal product ENTYVIO 108 mg (vedolizumab) administered subcutaneously is an alternative to the IV form of vedolizumab already available. Its role in the care pathway for ulcerative colitis is identical to that for the IV form. This medicinal product is a second or later-line treatment.

◗ In patients with previous failure to conventional therapies alone (second-line), the therapeutic alternatives are TNFα antagonists (adalimumab, infliximab and golimumab) and intravenous vedolizumab.
In patients with previous failure to conventional therapies and TNFα antagonists (third-line treatment), the currently reimbursable alternatives are intravenous vedolizumab and tofacitinib.

Public health impact

Considering:

- the seriousness and prevalence of ulcerative colitis, a serious and incapacitating chronic disease that can significantly impair quality of life and with high morbidity due to the frequency of acute flare-ups, its complications and recourse to surgery;
- the partially met medical need,
- the partial response to the identified need in terms of clinical remission despite the absence of comparison with intravenous vedolizumab but given the pharmacokinetic data available,
- the absence of robust data on quality of life, colectomy and corticosteroid-free remission,
- the potential benefit in terms of the organisation of care and the patient's care pathway, enabling avoidance of hospitalisations, but not demonstrated at this stage,

subcutaneous ENTYVIO 108 mg (vedolizumab) is unlikely to have an additional impact on public health for the management of ulcerative colitis.

Considering all these elements, the Committee deems that the clinical benefit of ENTYVIO 108 mg (vedolizumab) solution for injection in pre-filled syringe and in pre-filled pen is substantial in the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

Crohn's disease

◗ Crohn's disease is a chronic inflammatory bowel disease. It progresses by flare-ups interspersed with remissions. It is a debilitating condition which can lead to a marked deterioration in quality of life.

◗ The proprietary medicinal product ENTYVIO 108 mg (vedolizumab) administered subcutaneously is part of a symptomatic treatment regimen.

◗ Its efficacy/adverse effects ratio is high.

◗ The proprietary medicinal product ENTYVIO 108 mg (vedolizumab) administered subcutaneously is an alternative to the vedolizumab IV form already available. Its role in the care pathway for Crohn's disease is identical to that for the IV form. It should be reserved for use as third-line treatment only, i.e., for patients with previous failure (inadequate response, loss of response, contraindication or intolerance) to conventional therapy and at least one TNFα antagonist. In TNFα antagonist-naive patients (second-line treatment following previous failure of conventional treatments), in the absence of a comparison with a TNFα antagonist, the role of this medicinal product compared to TNFα antagonists cannot be specified.

◗ In patients with previous failure to conventional therapies alone (second-line treatment), the therapeutic alternatives are TNFα antagonists.
In patients with previous failure to conventional therapies and TNFα antagonists (third-line treatment), the therapeutic alternatives are IV vedolizumab and ustekinumab.

◗ Public health impact

Considering:

- the seriousness of Crohn's disease, a serious and incapacitating chronic disease that significantly impairs quality of life and with high morbidity due to the frequency of acute flare-ups, its complications and recourse to surgery,
- the low prevalence of moderately to severely active forms with previous failure to conventional therapies and TNFα antagonists,
- the partially met medical need,
- the partial response to the identified need despite the absence of comparison with IV vedolizumab but given the pharmacokinetic data available,
- the absence of robust data on quality of life, colectomy and corticosteroid-free remission,
- a potential benefit in terms of the organisation of care and the patient's care pathway, enabling avoidance of hospitalisations, but not demonstrated at this stage,

subcutaneous ENTYVIO 108 mg (vedolizumab) is unlikely to have an additional impact on public health for the management of Crohn's disease.

Given all these elements, the Committee deems that the clinical benefit of subcutaneous ENTYVIO 108 mg (vedolizumab) in the treatment of moderately to severely active Crohn's disease is:

- **substantial in patients with previous failure (inadequate response, loss of response, contraindication or intolerance) to conventional therapy (corticosteroids or immunosuppressants) and at least one TNFα antagonist,**
- **insufficient to justify public funding cover in view of the available therapies in TNFα antagonist-naive patients, in the absence of comparative studies versus TNFα antagonists.**

Conclusion

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indications:

- **treatment of adult patients with moderately to severely active ulcerative colitis 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 (second and third-line treatment);**
- **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 conventional therapy and at least one tumour necrosis factor-alpha (TNFα) antagonist (third-line treatment).**

and at the MA dosages.

◗ **Recommended reimbursement rate: 65%**

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the treatment of TNFα antagonist-naive adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy .

Clinical Added Value

Ulcerative colitis

Considering:
- **demonstration of the superiority of subcutaneous vedolizumab compared to placebo in terms of clinical remission at week 52, in patients with moderately to severely active Crohn's disease with previous failure to conventional therapy or a TNFα antagonist;**
- **pharmacokinetic data having compared subcutaneous vedolizumab to intravenous vedolizumab;**
- **a safety profile that is similar overall to that of intravenous vedolizumab, except for the occurrence of injection site reactions with the subcutaneous form;**
- **the absence of long-term efficacy and safety data enabling confirmation of the short-term data,**

ENTYVIO 108 mg (vedolizumab) solution for injection in pre-filled syringe and in pre-filled pen provides no clinical added value (CAV V) compared to intravenous ENTYVIO 300 mg (vedolizumab) in the treatment of adult patients with moderately to severely active ulcerative colitis with previous failure (inadequate response, loss of response, contraindication or intolerance) to either conventional therapy or a TNFα antagonist.

Crohn's disease

Considering:
- **demonstration of the superiority of subcutaneous vedolizumab compared to placebo in terms of clinical remission at week 52, in patients with moderately to severely active Crohn's disease with previous failure to conventional therapy or a TNFα antagonist;**
- **pharmacokinetic data having compared subcutaneous vedolizumab to intravenous vedolizumab;**
- **a safety profile that is similar overall to that of intravenous vedolizumab, except for the occurrence of injection site reactions with the subcutaneous form;**
- **the absence of long-term efficacy and safety data enabling confirmation of the short-term data;**

ENTYVIO 10 mg (vedolizumab) solution for injection in pre-filled syringe and in pre-filled pen provides no clinical added value (CAV V) compared to intravenous ENTYVIO 300 mg (vedolizumab) in the third-line treatment of adult patients with moderately to severely active Crohn's disease with previous failure (inadequate response, loss of response, contraindication or intolerance) to conventional therapy and at least one TNFα antagonist.