Key points

Favourable opinion for reimbursement in the Marketing Authorization (MA) indications for Crohn’s disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis.

In plaque psoriasis:
Favourable opinion for reimbursement only in adults with severe chronic plaque psoriasis, defined by:
- failure (insufficient response, contraindication or intolerance) of at least two treatments including non-biological systemic treatments and phototherapy
- and an extensive form and/or significant psychosocial impact.
Unfavourable opinion for reimbursement in other situations.

What therapeutic improvement?

No clinical added value compared to infliximab administered intravenously (REMICADE and its biosimilars, including REMSIMA 100 mg) in the treatment of Crohn’s disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis.
In accordance with its SPC, treatment with subcutaneous REMSIMA 120 mg (infliximab) must be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of the diseases for which REMSIMA is indicated. This treatment should be initiated following induction treatment with 2 infusions of REMSIMA 100 mg IV at 2-week intervals.

**Crohn’s disease**
Management of Crohn’s disease involves aminosalicylates, such as mesalazine or sulfasalazine, corticosteroids and immunosuppressants, including azathioprine, 6-mercaptopurine and methotrexate. The use of a TNFα antagonist (infliximab and adalimumab) with an MA in moderate to severe forms of Crohn’s disease 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 (integrin antagonist) and ustekinumab (anti-IL12/23) should only be used as third-line therapy (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**
Subcutaneous REMSIMA 120 mg (infliximab) is a second-line treatment for active moderate to severe forms of Crohn’s disease and in fistulised active forms in the event of failure of corticosteroids and/or immunosuppressants.

**Ulcerative colitis**
Following an inadequate response or intolerance to conventional topical or oral therapies (5-aminosalicylates, corticosteroids and immunosuppressants, such as azathioprine, methotrexate), biological systemic treatments can be used, starting with TNFα antagonists (as second-line treatment): infliximab, adalimumab golimumab.

Three other biological systemic treatments are available: vedolizumab (integrin antagonist), which can be prescribed as second or third-line treatment (following an inadequate response to TNFα antagonists) and tofacitinib (JAK inhibitor, oral route) and ustekinumab (anti-IL12/IL23) as third-line treatment following an inadequate response to TNFα antagonists or vedolizumab.

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.

Specifically in rare forms of ulcerative colitis, following the failure of first-line treatment with corticosteroids, ciclosporin (off-label) or infliximab can be prescribed as a last resort before surgery (subtotal colectomy or colectrectomy).

In clinical practice, in the event of no response, loss of response (tachyphylaxis) or intolerance to TNFα antagonists, depending on the nature of the failure, the options are as follows:

- increasing the doses or administration frequency of TNFα antagonists,
- use of another TNFα antagonist,
- as last-line therapy, use of vedolizumab and tofacitinib.

**Role of the medicinal product in the care pathway**
Subcutaneous REMSIMA 120 mg (infliximab) is a second-line treatment for moderately to severely active ulcerative colitis in the event of failure (inadequate response, contraindication or intolerance) of treatment including corticosteroids, azathioprine and/or 6 mercaptopurine.
Ankylosing spondylitis

Medicinal treatment is based on the first-line use of NSAIDs (prescription on demand, adapted to the patient, up to the maximum dose) as a symptomatic treatment in the event of flare-ups only. In the event of failure or an inadequate effect of an NSAID used at the maximum tolerated dose, a switch of NSAID can be performed. Adjuvant therapies such as analgesics can be combined with the NSAIDs for residual pain but systemic or local corticosteroid therapy is not justified in axial forms. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (e.g., methotrexate, leflunomide, sulfasalazine) only appear to be effective in forms with peripheral joint involvement refractory to symptomatic treatment. Their efficacy in purely axial forms has not been demonstrated. In ankylosing spondylitis, in the event of failure of NSAIDs, there are five TNFα antagonists (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) and two IL17 inhibitors (ixekizumab and secukinumab) available. In the event of loss of response, primary inefficacy or intolerance to a first TNFα inhibitor, a rotation to a second TNFα inhibitor or a switch to an IL17 inhibitor are alternatives deemed to be beneficial.

Role of the medicinal product in the care pathway

Subcutaneous REMSIMA 120 mg (infliximab) is a second-line treatment for severe, active ankylosing spondylitis, in the event of failure, an inadequate response or intolerance or contraindication to NSAIDs.

Psoriatic arthritis

In the absence of contraindications, NSAIDs are the first-line symptomatic treatments. Local injections of corticosteroids at symptomatic sites (arthritis and enthesitis, in particular) may be considered. In the majority of cases, systemic corticosteroid therapy is not justified for the treatment of axial signs. As regards conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs): methotrexate, leflunomide and sulfasalazine (off-label), these can be considered in the event of peripheral arthritis refractory to symptomatic treatment. However, these treatments are not currently indicated in isolated axial or enthesitic signs. If these treatments fail, biologic therapies may be offered: TNFα antagonists (adalimumab, etanercept, certolizumab pegol and golimumab), an IL12/23 inhibitor (ustekinumab) and IL17 inhibitors (secukinumab and ixekizumab). Tofacitinib (janus kinase inhibitors) is also an option. Given experience of around 15 years for TNFα inhibitors (MA for etanercept dating back to 2003) and demonstration of clinical efficacy on peripheral and axial involvement and joint destruction with this class of medicinal products, TNFα antagonists should be favoured as first-line therapy. In certain specific cases, the phosphodiesterase 4 inhibitor, apremilast, may be proposed. In the event of inefficacy or intolerance to a first biological medicinal product, following analysis of the reasons for the failure, a second biologic may be considered.

Role of the medicinal product in the care pathway

Subcutaneous REMSIMA 120 mg (infliximab) is a second-line treatment for psoriatic arthritis, alone or in combination with methotrexate in active forms of the disease and in the event of failure, an inadequate response or intolerance or contraindication to DMARDs.

Plaque psoriasis

Current psoriasis treatments do not result in the definitive cure of the condition, but allow for transient and more or less complete disappearance of the lesions. The therapeutic arsenal includes local and general treatments. Local treatments can be used alone or combined either with each other or with general treatments. In the most severe forms, systemic treatments can be used: methotrexate (reference treatment), ciclosporin as an alternative to methotrexate, retinoids (acitretin) in certain clinical forms or in combination with phototherapy. If these first-line systemic treatments fail or are not tolerated, systemic biological treatments are recommended: TNFα inhibitors (adalimumab, etanercept), IL12/23 interleukin inhibitors (ustekinumab), IL17 inhibitors (secukinumab, ixekizumab), IL17 receptor inhibitors (brodalumab) and IL23 inhibitors (rizankizumab, guselkumab and tildrakizumab). Adalimumab (TNFα inhibitor) and ustekinumab (IL12/23 inhibitors) are the first-line systemic biological treatments. The role of apremilast (phosphodiesterase inhibitor 4) remains poorly defined with results significantly inferior to biological treatments. The current treatment strategy is "rotational" between the different alternatives, the choice of treatment being guided by patient and disease characteristics (concomitant disease, extent of lesions, previous treatment history) and those of the proprietary medicinal product (adverse effects, cumulative dose).
**Role of the medicinal product in the care pathway**
REMSIMA 120 mg (infliximab) SC, like other systemic biologic therapies, should be reserved for the
treatment of adult patients with severe, chronic plaque psoriasis, defined by:
- failure (insufficient response, contraindication or intolerance) of at least two treatments including
  non-biological systemic treatments and phototherapy
- and an extensive form and/or significant psychosocial impact.

**For all the indications**, in the absence of comparison with other biologics, the role of REMSIMA 120
mg (infliximab) SC in the care pathway cannot be specified compared to these medicinal products.

### Special recommendations

Given the risk of hypersensitivity reactions with infliximab by the SC route (see paragraph 4.4 of the
SPC), the Transparency Committee recommends that, as for other biologics, the first subcutaneous
injection of this drug be performed in an appropriate care structure.

As indicated in the SPC, the Committee draws prescribers’ attention to the fact that there is insufficient
information regarding the switching of patients having received intravenous infusions of infliximab
higher than 5 mg/kg every 8 weeks as maintenance treatment to the subcutaneous formulation of
infliximab (REMSIMA).
COMMITTEE’S CONCLUSIONS

Clinical benefit

Crohn’s disease

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

- REMSIMA 120 mg (infliximab) by the subcutaneous route (SC) is a symptomatic treatment.

- Considering:
  - demonstration, in an open-label phase I study of the non-inferiority of infliximab SC compared to infliximab IV in terms of pre-dose residual serum concentrations in patients with Crohn’s disease or ulcerative colitis without robust demonstration of the non-inferiority on a clinical endpoint,
  - demonstration of the non-inferiority in terms of clinical response of infliximab SC compared to infliximab IV in the initial MA indication (rheumatoid arthritis) and,
  - a short-term safety profile (data available up to week 54) globally similar to that of the IV route, except for more frequent local reactions at the injection site with the SC route but uncertainties with respect to long-term safety, due to overexposure to infliximab with the SC route,

on the basis of currently available data, the efficacy/adverse effects ratio of this proprietary medicinal product is moderate.

- There are therapeutic alternatives by the intravenous (in particular, infliximab) and subcutaneous routes.

- REMSIMA 120 mg (infliximab) SC is a second-line treatment for moderately to severely active forms of Crohn’s disease and fistulised active forms of Crohn’s disease in the event of failure of corticosteroids and/or immunosuppressants.

Public health impact

Considering:
- the seriousness of this disabling chronic disease, which causes an impairment in quality of life,
- the low prevalence of severe forms not having responded to conventional treatments,
- the inadequately met medical need,
- the absence of a demonstrated impact in terms of morbidity, the assessment of clinical efficacy based solely on pharmacokinetic data in patients with Crohn’s disease or ulcerative colitis (non-inferiority of the subcutaneous route compared to the intravenous route in terms of residual mean serum concentrations before administration),
- the absence of robust quality of life data,
- the absence of a comparison with the other available treatments,
- a potential benefit in terms of the organisation of care and the patient’s care and/or life pathway, enabling avoidance of hospitalisations, but limited to certain patients already treated with IV infliximab or in whom treatment with infliximab must be initiated, not demonstrated at this stage,

REMSIMA 120 mg (infliximab) SC is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of subcutaneous REMSIMA 120 mg (infliximab) is moderate in the MA indications.
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.

- REMSIMA 120 mg (infliximab) by the subcutaneous route (SC) is a symptomatic treatment.

Considering:
- demonstration, in an open-label phase I study of the non-inferiority of infliximab SC compared to infliximab IV in terms of pre-dose residual serum concentrations in patients with Crohn’s disease or ulcerative colitis without robust demonstration of the non-inferiority on a clinical endpoint,
- demonstration of the non-inferiority in terms of clinical response of infliximab SC compared to infliximab IV in the initial MA indication (rheumatoid arthritis) and,
- a short-term safety profile (data available up to week 54) globally similar to that of the IV route, except for more frequent local reactions at the injection site with the SC route but uncertainties with respect to long-term safety, due to overexposure to infliximab with the SC route,

on the basis of currently available data, the efficacy/adverse effects ratio of this proprietary medicinal product is moderate.

- There are therapeutic alternatives by the intravenous (in particular, infliximab), subcutaneous and oral routes.

- REMSIMA 120 mg (infliximab) SC is a second-line treatment for moderately to severely active ulcerative colitis in the event of failure (inadequate response, contraindication or intolerance) of treatment including corticosteroids, azathioprine and/or 6 mercaptopurine.

Public health impact

Considering:
- the seriousness of this disabling disease, which causes an impairment in quality of life,
- the low prevalence of severe forms not having responded to conventional treatments,
- the partially met medical need,
- the absence of a demonstrated impact in terms of morbidity, the assessment of clinical efficacy based on pharmacokinetic data in patients with Crohn’s disease or ulcerative colitis (non-inferiority of the subcutaneous route compared to the intravenous route in terms of residual mean serum concentrations before administration),
- the absence of robust quality of life data,
- the absence of a comparison with the other treatments,
- a potential benefit in terms of the organisation of care and the patient’s care pathway, enabling avoidance of hospitalisations, but limited to certain patients already treated with IV infliximab or in whom treatment with infliximab must be initiated, not demonstrated at this stage,

REMSIMA 120 mg (infliximab) SC is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of subcutaneous REMSIMA 120 mg (infliximab) is moderate in the MA indication.
Ankylosing spondylitis

- Ankylosing spondylitis is a chronic condition, some forms of which can be serious and disabling.
- REMSIMA 120 mg (infliximab) by the subcutaneous route (SC) is a symptomatic treatment.
- Considering:
  - the absence of data assessing infliximab SC in this indication but taking into account the pharmacokinetic data available versus infliximab IV in other indications (rheumatoid arthritis, Crohn’s disease and ulcerative colitis) and demonstration of the non-inferiority in terms of clinical response of infliximab SC compared to infliximab IV in rheumatoid arthritis and,
  - the short-term safety profile (data available up to week 54) globally similar to that of the IV route, except for more frequent local reactions at the injection site with the SC route but uncertainties with respect to long-term safety, due to greater exposure to infliximab by the SC route than with the IV route,
  on the basis of currently available data, the efficacy/adverse effects ratio of this proprietary medicinal product is moderate.
- There are therapeutic alternatives by the intravenous (in particular, infliximab) and subcutaneous routes.
- REMSIMA 120 mg (infliximab) SC is a second-line treatment for severe, active ankylosing spondylitis, in the event of failure, an inadequate response or intolerance or contraindication to NSAIDs.

Public health impact

Considering:
- the seriousness of this disabling chronic disease, which causes an impairment in quality of life,
- the low prevalence of severe forms not having responded to conventional treatments,
- the partially met medical need,
- the absence of demonstrated impact in terms of morbidity and quality of life given the absence of clinical data in adults with ankylosing spondylitis,
- a potential benefit in terms of the organisation of care and the patient’s care pathway, enabling avoidance of hospitalisations, but limited to certain patients already treated with IV infliximab or in whom treatment with infliximab must be initiated, not demonstrated at this stage,
  REMSIMA 120 mg (infliximab) SC is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of subcutaneous REMSIMA 120 mg (infliximab) is moderate in the MA indication.

Psoriatic arthritis

- Psoriatic arthritis is a chronic disease, which can be serious and disabling in certain cases.
- REMSIMA 120 mg (infliximab) by the subcutaneous route (SC) is a symptomatic treatment.
- Considering:
  - the absence of data assessing infliximab SC in this indication but taking into account the pharmacokinetic data available versus infliximab IV in other indications (rheumatoid arthritis, Crohn’s disease and ulcerative colitis) and demonstration of the non-inferiority in terms of clinical response of infliximab SC compared to infliximab IV in rheumatoid arthritis and
  - the short-term safety profile (data available up to week 54) globally similar to that of the IV route, except for more frequent local reactions at the injection site with the SC route but uncertainties with respect to long-term safety, due to greater exposure to infliximab by the SC route than with the IV route,
  on the basis of currently available data, the efficacy/adverse effects ratio of this proprietary medicinal product is moderate.
There are therapeutic alternatives by the intravenous (in particular, infliximab), subcutaneous and oral routes.

REMSIMA 120 mg (infliximab) SC is a second-line treatment for psoriatic arthritis, alone or in combination with methotrexate in active forms of the disease and in the event of failure, an inadequate response, intolerance or contraindication to DMARDs.

**Public health impact**

Considering:
- the seriousness of this disabling chronic disease, which causes an impairment in quality of life,
- its low prevalence not having responded to conventional treatments,
- the partially met medical need,
- the absence of demonstrated impact in terms of morbidity and quality of life given the absence of data in adults with psoriatic arthritis,
- a potential benefit in terms of the organisation of care and the patient’s care pathway, enabling avoidance of hospitalisations, but limited to certain patients already treated with IV infliximab or in whom treatment with infliximab must be initiated, not demonstrated at this stage,

REMSIMA 120 mg (infliximab) SC is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of subcutaneous REMSIMA 120 mg (infliximab) is moderate in the MA indication.

**Plaque psoriasis**

- Psoriasis is a chronic inflammatory skin condition, usually benign, that can, in its moderate to severe forms, have a significant impact on quality of life.

- REMSIMA 120 mg (infliximab) by the subcutaneous route (SC) is a symptomatic treatment.

Considering:
- the absence of data assessing infliximab SC in this indication but taking into account the pharmacokinetic data available versus infliximab IV in other indications (rheumatoid arthritis, Crohn's disease and ulcerative colitis) and demonstration of the non-inferiority in terms of clinical response of infliximab SC compared to infliximab IV in the initial MA indication (rheumatoid arthritis) and
- the short-term safety profile (data available up to week 54) globally similar to that of the IV route, except for more frequent local reactions at the injection site with the SC route but uncertainties with respect to long-term safety, due to greater exposure to infliximab by the SC route than with the IV route,

on the basis of currently available data, the efficacy/adverse effects ratio of this proprietary medicinal product is moderate.

- There are therapeutic alternatives by the intravenous (in particular, infliximab) and subcutaneous routes.

- REMSIMA 120 mg (infliximab) SC, like other systemic biologic therapies, should be reserved, in the treatment of plaque psoriasis, for the treatment of adult patients with severe, chronic plaque psoriasis, defined by:
  - failure (insufficient response, contraindication or intolerance) of at least two treatments including non-biological systemic treatments and phototherapy
  - an extensive form and/or significant psychosocial impact.

**Public health impact**

Considering:
- the seriousness of this disabling chronic disease, which causes an impairment in quality of life,
- the low prevalence of severe forms not having responded to first-line systemic treatments,
- the partially met medical need despite the numerous medicinal products available, due to tachyphylaxis phenomena, intolerance and contraindications,
- the absence of demonstrated impact in terms of morbidity and quality of life given the absence of data in adults with plaque psoriasis,
- a potential benefit in terms of the organisation of care and the patient’s care pathway, enabling avoidance of hospitalisations, but limited to certain patients already treated with IV infliximab or in whom treatment with infliximab must be initiated, not demonstrated at this stage,

REMSIMA 120 mg (infliximab) SC is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of subcutaneous REMSIMA 120 mg (infliximab) is:

- moderate in the treatment of severe chronic plaque psoriasis, defined by:
  - failure (insufficient response, contraindication or intolerance) of at least two treatments including non-biological systemic treatments and phototherapy
  - and an extensive form and/or significant psychosocial impact.
- insufficient to justify public funding cover in all other clinical situations.

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 marketing authorisation indications and dosages for Crohn’s disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis.

In plaque psoriasis, 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 only in the treatment of adult patients with severe chronic plaque psoriasis, defined by:
  - failure (insufficient response, contraindication or intolerance) of at least two treatments including non-biological systemic treatments and phototherapy
  - and an extensive form and/or significant psychosocial impact.
- 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 other situations.

Clinical Added Value

Considering:

- demonstration of the non-inferiority of infliximab by the subcutaneous route (SC), as maintenance therapy at a dosage of 120 mg every 2 weeks, compared to infliximab by the intravenous route (IV), at a dose of 5 mg/kg every 8 weeks, on a pharmacokinetic parameter (average pre-dose residual serum concentrations at week 22) in patients with Crohn’s disease or ulcerative colitis,
- demonstration of the non-inferiority of infliximab SC compared to infliximab IV on a clinical endpoint in the initial MA indication (rheumatoid arthritis),
- the short-term safety profile (data available up to week 54) globally similar to that of the IV route, except for more frequent local reactions at the injection site with the SC route,

but taking into account:

- uncertainties with respect to long-term safety, due to greater exposure to infliximab by the SC route than with the IV route,
- the absence of comparative clinical data for infliximab SC versus infliximab IV in Crohn’s disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis,
subcutaneous REMSIMA 120 mg (infliximab) provides no clinical added value (CAV V) compared to infliximab administered intravenously (REMICADE and its biosimilars, including REMSIMA 100 mg) in the treatment of Crohn’s disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis.