HAUTE AUTORITÉ DE SANTÉ

ASSESSING HEALTH TECHNOLOGIES

OPINION ON MEDICINAL PRODUCTS

belatacept

NULOJIX 250 mg,

powder for dilutable solution for perfusion

New indication

Adopted by the Transparency Committee on 21 September 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Positive opinion for reimbursement in the prevention of graft rejection, in combination with corticosteroids and mycophenolic acid, in adult EBV+ kidney transplant patients in the **context of conversion from a treatment including a CNI at least 6 months post-transplant**.

Therapeutic improvement?

No progress in the therapeutic strategy for the prevention of graft rejection in adult kidney transplant recipients, converting from treatment with a calcineurin inhibitor (CNI) at least 6 months post-transplant.

Role in therapeutic strategy?

Immunosuppression protocols are based on two phases of treatment:

- an initial "induction" phase with stronger immunosuppression, based on the administration of depleting or non-depleting monoclonal (anti-CD3) or polyclonal (anti-lymphocyte serum) antibodies (basiliximab or daclizumab)
- a maintenance phase based on five therapeutic classes, often combined:
  - corticosteroids;
  - anticalcineurins: cyclosporin and preferably tacrolimus;
  - antimetabolics: azathioprine, mycophenolate mofetil and mycophenolic acid;
  - mTOR inhibitors: sirolimus and everolimus;
  - the T-cell co-stimulation inhibitor: belatacept.

The maintenance phase of immunosuppression usually involves a combination of two or three immunosuppressive drugs, which may be modified according to the clinical situation. **The most commonly used protocol combines an anticalcineurin (preferably tacrolimus) with an anti-metabolic agent.**

Immunosuppression protocols are prescribed according to numerous immunological parameters, including the initial compatibility between the host and the graft, the occurrence of rejection or infection, and the recipient's age.

According to the 2021 European Association of Urology recommendations, when discontinuation of the current anticalcineurin treatment is deemed necessary by the practitioner, different treatment options may be considered for conversion, depending on the clinical situation justifying the discontinuation: a different anticalcineurin agent, mTOR inhibitors, antimetabolics or belatacept.

NULOJIX (belatacept) is the only immunosuppressant available as a dilutable solution for intravenous infusion (monthly infusion).

Role of the medicinal product

Based on the results observed in studies IM103010 and IM103016, although of low methodological quality, the Committee considers that NULOJIX (belatacept), in combination with corticosteroids and mycophenolic acid (MPA), is a first-line option for the prevention of graft rejection in adult kidney transplant patients in conversion to a maintenance therapy with a CNI, at least 6 months post-transplant.

In the absence of comparative data, the role of NULOJIX (belatacept) in relation to other treatment options that may be considered for conversion from a CNI, in accordance with the latest European recommendations, cannot be determined.

Given the data suggesting less renal toxicity in patients who have converted to belatacept compared to patients continuing with a CNI, as already observed in studies of de novo transplant patients treated with belatacept compared to ciclosporin, NULOJIX (belatacept) may be of particular interest in patients with nephrotoxicity.

A higher risk of acute rejection was also observed after conversion to belatacept, particularly at the start of treatment, bearing in mind that patients at high immunological risk were excluded from the studies. In line with the SCP, the Committee underlines that more frequent monitoring for acute

rejection is therefore recommended for at least 6 months after conversion to belatacept, and that conversion in patients at high immunological risk should only be considered if the potential benefits are considered to outweigh the risks.

As a reminder, belatacept is contraindicated in transplant patients who are seronegative or of unknown serostatus for Epstein-Barr virus (EBV) due to the risk of developing a post-transplant lymphoproliferative syndrome (PTLS).

Committee's conclusions

Clinical Benefit

- Immunosuppressive treatments, associated with organ transplants, are administered in clinical situations of life-threatening severity.
- NULOJIX (belatacept) is used as part of a preventive treatment with other immunosuppressants.
- In conversion from treatment with a calcineurin inhibitor (CNI) at least 6 months post-transplant, it has a substantial efficacy/adverse effect ratio **in EBV+ patients** and in combination.
- This product is a first-line treatment for the prevention of graft rejection in adult kidney transplant patients in conversion from a CNI maintenance therapy at least 6 months post-transplant.
- Therapeutic alternatives are available, particularly ciclosporin and tacrolimus.
- **Public health benefit**

Considering:

- the severity of kidney transplant rejection and its prevalence,
- the partially covered medical need in patients selected for conversion from a CNI,
- the partial response to the identified, partially met medical need due to:
  - the expected additional impact on morbidity and mortality in terms of preservation of renal function, although the methodological quality of the evidence is very low and does not enable any robust conclusion to be drawn to date, and an increased risk of acute rejection,
  - the lack of evidence of an additional impact on quality of life,

NUCALA (belatacept) is not likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the actual clinical benefit of NULOJIX (belatacept) is SUBSTANTIAL in the prevention of graft rejection in adult renal transplant patients undergoing conversion from a treatment including a CNI at least 6 months after transplantation.

The Committee approves inclusion in the list of proprietary medicinal products approved for community use for the extension of the marketing authorisation indication and at the marketing authorisation dosages.

Clinical Added Value

Considering:

- the available studies that evaluated the benefit of converting from a CNI to belatacept versus continuing with a CNI, which were of poor methodological quality as they were purely descriptive studies with no statistical comparisons between the groups provided for in the protocol, enabling no formal conclusion as to the relative efficacy of these two strategies,
- the results observed in these studies, which suggest, in particular, an improvement in renal function following conversion, but no benefit in terms of patient and graft survival, and an increased risk of acute graft rejection,
- the lack of comparison with other treatment options that may be considered for conversion from a CNI according to the latest European recommendations, in particular m-TOR inhibitors,

the Transparency Committee deems that NULOJIX (belatacept) **provides no clinical added value (CAV V)** in the prevention of graft rejection in renal transplantation in the context of conversion from a CNI.