HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

2 JUNE 2021

The legally binding text is the original French opinion version

luspatercept

REBLOZYL 25 mg powder for solution for injection

REBLOZYL 75 mg powder for solution for injection

First assessment

Key points

Favourable opinion for reimbursement in the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, without 5q deletion, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.

Unfavourable opinion for reimbursement in the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic MDS with ring sideroblasts, with 5q deletion, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.

What therapeutic improvement?

Therapeutic improvement in the management of the disease.

Role in the care pathway?

The therapeutic management of patients with low-risk MDS is primarily based on the correction of cytopenias - mainly anaemia - which have a major impact on patients and may require repeated red cell concentrate transfusions.

When cytopenia is moderate or asymptomatic, no treatment may be favoured.

In the event of symptomatic anaemia, first-line treatment is based on high-dose recombinant EPO alone or in combination with G-CSF in patients with ≤10 g/dl Hb and poor clinical tolerance to this anaemia, even if they are not transfused. A treatment response is observed within three months; in the event of inefficacy after this period, treatment should be stopped. It should be noted that only the epoietin alfa EPREX and its biosimilar BINOCRIT have a specific MA in this indication in monotherapy (without G-CSF).

In the event of failure of EPO:

- Red cell concentrate (RCC) transfusions should be used following the failure of EPO and in the absence of other therapeutic alternatives. They are associated with a deterioration in quality of life, serious complications (particularly cardiovascular) and toxicity due to iron overload.
- Lenalidomide (REVLIMID) is indicated only in adult patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q (del 5q) cytogenetic abnormality when other therapeutic options are insufficient or inadequate.
- Other therapeutic options are cited by the national and European guidelines in specific populations but do not have a validated MA in France at present.

It should be noted that allogeneic haematopoietic stem cell transplantation (HSCT) is currently the only curative treatment, reserved for patients with high-risk MDS, with an HSC donor and aged less than 65-70 years.

Role of REBLOZYL (luspatercept) in the care pathway:

Within the reimbursement scope (without 5q deletion in the event of an inadequate response to or ineligibility for EPO therapy)

In view of:

- demonstration of the efficacy of REBLOZYL (luspatercept) compared to placebo for the endpoint of short-term achievement of transfusion independence at 24 and 48 weeks (with a small sample of patients remaining in the placebo group (n=12) for this last analysis), in patients not having responded to EPO, with transfusion-dependent anaemia and without 5q deletion,
- the comparison conducted versus placebo in a context in which the great majority of patients included (n=218/229; 95%) had previously received an erythropoiesis-stimulating agent, almost all of whom (n= 213/218; 98%) were refractory, which is therefore acceptable,
- the non-inclusion of patients presenting MDS associated with a chromosomal 5q deletion in the same study,

REBLOZYL (luspatercept) is a second-line treatment following an inadequate response to erythropoietin-based treatment or in the event of ineligibility for this treatment, in adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, without 5q deletion.

Within the scope included in the MA but not retained for reimbursement:

In other patients within the scope of the MA indication for myelodysplastic syndrome (corresponding to patients with 5q deletion), these patients not having been included in the MEDALIST study, and consequently in the absence of data in this subpopulation eligible for lenalidomide, REBLOZYL (luspatercept) has no role in the care pathway.

It is highlighted that, in accordance with the SPC, subcutaneous injections of REBLOZYL (luspatercept) every three weeks should be administered by a healthcare professional. The recommended maximum volume of medicinal product per injection site is 1.2 mL. If more than 1.2 mL is required, the total volume should be divided and administered across separate sites.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Myelodysplastic syndromes (MDS) are clonal disorders of the pluripotent or myeloid stem cells, characterised by ineffective haematopoiesis, responsible for blood cytopenias. They progress to acute myeloid leukaemia (AML) in 30 to 40% of cases and represent the most common pre-leukaemia condition in adults. The median survival for patients with very low, low or intermediate-risk MDS is estimated to be between 3 and 8.8 years.

◗ The proprietary medicinal product REBLOZYL (luspatercept) is a symptomatic medicinal product.

◗ Considering:

- demonstration of the superiority of luspatercept compared to placebo assessed in a randomised, double-blind study in RCC transfusion-dependent patients with very low, low or intermediate-risk MDS with ring sideroblasts, without 5q deletion, predominantly refractory (93%) to erythropoiesis-stimulating agents for the percentages of patients achieving red cell concentrate transfusion independence:
    - ≥ 8 consecutive weeks during the initial 24-week treatment phase (primary endpoint), with a moderate effect size: 37.9% in the luspatercept group *versus* 13.2% in the placebo group, i.e., an absolute difference of 24.6%
    - ≥ 12 consecutive weeks:
        - throughout the 48-week treatment period (ranked secondary endpoint): 33.3% *versus* 11.8%, i.e., an absolute difference of 21.4%
        - during the initial 24-week treatment phase (ranked secondary endpoint): 28.1% *versus* 7.9%, i.e., an absolute difference of 20.0%
- the absence of robust comparative data *versus* placebo for the response duration (unranked secondary endpoint) and changes in haemoglobin,
- the absence of robust quality of life data, which is regrettable in this disease,
- uncertainties concerning the long-term maintenance of efficacy, with an ad hoc analysis at a median follow-up of 26 months having reported a luspatercept discontinuation rate of 44% of patients treated due to lack of efficacy,
- the safety profile observed after a median treatment follow-up limited to around 12.7 months

the efficacy/adverse effects ratio is high in adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, without 5q deletion, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.
The efficacy/adverse effects ratio has not been established in patients with 5q deletion in the absence of data in this sub-population.

◗ - In patients without 5q deletion: red cell concentrate (RCC) transfusions are the therapeutic alternative.
- In patients with 5q deletion: the proprietary medicinal product REVLIMID (lenalidomide) and RCC transfusions are therapeutic alternatives.

◗ REBLOZYL (luspatercept) is a second-line treatment following an inadequate response to erythropoietin-based treatment or in the event of ineligibility for this treatment, in adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, without 5q deletion.
In other patients within the scope of the MA indication for myelodysplastic syndrome (corresponding to patients with 5q deletion), these patients not having been included in the MEDALIST study, and consequently in the absence of data in this subpopulation, REBLOZYL (luspatercept) has no role in the care pathway.

Public health impact

Considering:

- the seriousness of the disease and its prevalence,
- the partially met medical need,
- the partial response to the identified need:
    - with an additional impact expected on morbidity and mortality in terms of achievement of transfusion independence ≥ 8 weeks and ≥ 12 weeks, but demonstrated in the short term (primary analysis at 24 weeks and ranked secondary analysis at 48 weeks with a small sample of patients remaining in the placebo group (n=12) for this last analysis); uncertainties concerning the long-term maintenance of efficacy remain, with an ad hoc analysis at a median follow-up of 26 months having reported a luspatercept discontinuation rate of 44% of patients treated due to lack of efficacy,
    - the lack of demonstrated impact on quality of life in a context in which this is severely impaired in this disease,
    - with an expected potential impact on the organisation of care and the patient's life pathway due to the reduction in transfusion burden and the number of associated hospitalisation days,

REBLOZYL (luspatercept) is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of REBLOZYL (luspatercept) is:

- **substantial in the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, without 5q deletion, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy;**
- **insufficient to justify its public funding cover in the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic MDS with ring sideroblasts, with 5q deletion, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.**

The Committee issues the following opinions:

- **favourable 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 adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, without 5q deletion, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy and at the MA dosages;**
- **unfavourable 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 adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, with 5q deletion, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy and at the MA dosages.**

◗ **Recommended reimbursement rate: 100%**

Clinical Added Value

Considering:

- **demonstration of the superiority of luspatercept compared to placebo** assessed in a randomised, double-blind study in RCC transfusion-dependent patients with very low, low or intermediate-risk MDS with ring sideroblasts, **without 5q deletion**, **predominantly refractory** (93%) to erythropoiesis-stimulating agents for **the percentages of patients achieving red cell concentrate transfusion independence**:
    - ≥ 8 consecutive weeks during the initial 24-week treatment phase (primary endpoint), with a moderate effect size: **37.9% in the luspatercept group *versus* 13.2% in the placebo group, i.e., an absolute difference of 24.6%** ((OR = 5.1; $CI_{95\%}$ [2.3; 11.3]; p< 0.0001),
    - ≥ 12 consecutive weeks:
        - throughout the 48-week treatment period (ranked secondary endpoint): 33.3% *versus* 11.8%, i.e., an absolute difference of 21.4% between the two groups (OR=4.0; $CI_{95\%}$ [1.8; 8.9]; p=0.0003,
        - during the initial 24-week treatment phase (ranked secondary endpoint): 28.1% *versus* 7.9%, i.e., an absolute difference of 20.0% between the two groups (OR = 5.1; $CI_{95\%}$ [2.0; 12.8]; p=0.0002),
- **the clinical relevance of achieving transfusion independence in this population with an unsatisfactory response to/ineligible for EPOs and with a severely impaired quality of life, as reported by patient associations,**

and despite:

- the absence of robust comparative data *versus* placebo for the response duration (unranked secondary endpoint) and changes in haemoglobin levels,
- the absence of robust quality of life data, which is regrettable in this disease,
- uncertainties concerning the long-term maintenance of efficacy, with an ad hoc analysis at a median follow-up of 26 months having reported a luspatercept discontinuation rate of 44% of patients treated due to lack of efficacy,
- the safety profile observed after a median treatment follow-up limited to around 12.7 months,

the Committee considers that REBLOZYL (luspatercept) provides a **minor clinical added value (CAV IV) in the therapeutic strategy for** the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, without 5q deletion, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.