HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
6 OCTOBER 2021

The legally binding text is the original French opinion version

caplacizumab
CABLIVI 10 mg powder and solvent for solution for infusion

New indication
Re-evaluation

Key points

Favourable opinion for reimbursement in the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.

Unfavourable opinion for reimbursement in adolescents of 12 years of age and older weighing at least 40 kg in this indication.

What therapeutic improvement?

In adults in combination with standard therapy including plasma exchange and immunosuppression, therapeutic improvement compared to standard treatment of the aTTP episode.

Role in the care pathway?

aTTP requires rapid diagnosis, its management constituting a therapeutic emergency for which daily plasma exchanges should be rapidly implemented in combination with immunosuppression (generally corticosteroids ± rituximab). The urgent initiation of plasma exchanges as soon as possible is essential, since these enable the supply of ADAMTS13, the elimination of abnormal von Willebrand factor (vWF) multimers and anti ADAMTS13 auto-antibodies. The confirmation of the diagnosis, provided by the measurement of ADAMTS13 activity, occurs after emergency treatment initiation.

Role of the medicinal product in the care pathway

In adults

CABLIVI (caplacizumab) is a first-line treatment for adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression. The available data does not enable the definition of a typology of patients derive a greater benefit from the treatment with CABLIVI (caplacizumab).

CABLIVI (caplacizumab) is active on the initial microthrombi formation phase. Treatment with CABLIVI (caplacizumab) should therefore be initiated early on during standard treatment including plasma exchanges and immunosuppression, upon clinical presumption of an aTTP episode, without waiting for confirmation.

CABLIVI (caplacizumab) is initiated by intravenous injection before plasma exchange, then continued by daily subcutaneous administration after each plasma exchange, for the entire duration of daily plasma exchange treatment, followed by daily subcutaneous injections for 30 days after termination of plasma exchange treatment. For patients in clinical remission and whose ADAMTS13 activity has normalised, no data concerning discontinuation before the end of the 30-day post-PE caplacizumab treatment is available.

In clinical studies, the relapse rate was higher at the end of treatment in patients receiving caplacizumab and maintaining an undetectable ADAMTS13 activity. Consequently, if, at the end of this 30-day period, signs indicate that disease activity has not been resolved, the immunosuppression treatment should be optimised and subcutaneous administration of CABLIVI (caplacizumab) should be continued until the signs of the underlying disease have been resolved (in particular sustained normalisation of ADAMTS13 activity). The phase 3 study (HERCULES - ALX0681-C301) scheduled weekly monitoring of the activity of this protease. There is no data available on the long-term efficacy, in particular on relapses, and safety of CABLIVI (caplacizumab).

In adolescents above 12 years of age weighing at least 40 kg

Given the very scarce clinical data available, based only on a small number of case studies published in the literature, and in the absence of conclusive clinical data concerning its efficacy and safety in this population, CABLIVI (caplacizumab) has no role in the care pathway in adolescents above 12 years of age weighing at least 40 kg.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

In adults

◗ An aTTP episode is serious, potentially leading to ischaemic events with significant clinical repercussions (in particular, stroke, myocardial infarction, kidney failure) and short-term threat to life without treatment, in young patients.

◗ CABLIVI (caplacizumab) is a curative medicinal product for aTTP.

◗ The efficacy/adverse effects ratio of CABLIVI (caplacizumab) is high in adults.

◗ The therapeutic alternative available is the standard treatment of aTTP episodes, including plasma exchanges in conjunction with immunosuppression.

◗ In adults, CABLIVI (caplacizumab) is a first-line treatment for aTTP episodes, administered in combination with standard treatment, including plasma exchanges in conjunction with immunosuppression.

Public health impact

Considering:

- the seriousness of the disease and its rarity,
- the medical need in adults partially met by CABLIVI (caplacizumab) administered in combination with treatment with plasma exchanges and immunosuppression.
- but in view of the response to the identified need provided by CABLIVI (caplacizumab), which remains partial, with:
    - the absence of an additional impact on morbidity and mortality demonstrated by the new data provided, derived from analysis of the CNR-MAT registry and the PMSI; this new data does not further support the efficacy of CABLIVI (caplacizumab) for relevant clinical endpoints, such as visceral pain and mortality, given the exploratory nature of the result concerning mortality in the analysis of the CNR-MAT registry, the absence of mortality data derived from the PMSI analysis and the absence of data provided concerning visceral pain in the analyses of the CNR-MAT registry and the PMSI,
    - the lack of demonstrated additional impact on quality of life in the absence of available data,
    - the absence of a demonstrated additional impact on the organisation of care in view of the new data provided derived from analysis of the CNR-MAT registry and the PMSI given the methodological biases identified,
    - the lack of demonstrated additional impact in terms of improvement of care and/or life pathway in the absence of available data,

CABLIVI (caplacizumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of CABLIVI (caplacizumab) is substantial in the MA indication for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.
The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication in adults, and at the MA dosages.

In adolescents above 12 years of age weighing at least 40 kg

◗ An aTTP episode is serious, potentially leading to ischaemic events with significant clinical repercussions (in particular, stroke, myocardial infarction, kidney failure) and short-term threat to life without treatment, in young patients.

◗ CABLIVI (caplacizumab) is a curative medicinal product for aTTP.

◗ Given the very scarce clinical data available, based only on a small number of case studies, and in the absence of conclusive clinical data concerning its efficacy and safety in this indication extension, the efficacy/adverse effects ratio of CABLIVI (caplacizumab) in the indication extension in adolescents above 12 years of age weighing at least 40 kg has been inadequately established.

◗ The therapeutic alternative available is the standard treatment of aTTP episodes, including plasma exchanges in conjunction with immunosuppression.

◗ Given the very scarce clinical data available, based only on a small number of case studies published in the literature, and in the absence of conclusive clinical data concerning its efficacy and safety in this population, CABLIVI (caplacizumab) has no role in the care pathway in adolescents above 12 years of age weighing at least 40 kg.

Public health impact

Considering:

- the seriousness of the disease and its rarity,
- the medical need partially met in adolescents by standard therapy including plasma exchange and immunosuppression,
- the absence of response provided by CABLIVI (caplacizumab) to the identified need, with
    - the absence of a demonstrated impact on morbidity and mortality and on quality of life in view of the data provided based only on an analysis of cases published in the literature and in the absence of data from a clinical study or pertinent registry analysis,
    - the lack of demonstrated impact on the organisation of care in the absence of data,
    - the lack of demonstrated additional impact in terms of improvement of care and/or life pathway in the absence of available data,

CABLIVI (caplacizumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of CABLIVI (caplacizumab) is insufficient in the MA indication extension, i.e. for the treatment of adolescents above 12 years of age weighing at least 40 kg experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.

The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in adolescents above 12 years of age weighing at least 40 kg, and at the MA dosages.

Clinical Added Value

In adults

Considering,

- the initial assessment of CABLIVI (caplacizumab) in aTTP in adults, which showed:
    - the superiority of CABLIVI (caplacizumab) compared to placebo, both in conjunction with plasma exchanges (PE) and immunosuppression, in a randomised, double-blind study, based on a biological endpoint, i.e., the time to normalisation of platelet levels (primary endpoint), with an additional effect size deemed to be modest (difference in medians of 4 hours 30 minutes, HR=1.55 [1.095; 2.195]; p=0.0099),
    - the superiority of CABLIVI compared to placebo for one of the ranked secondary endpoints, i.e. the percentage of patients presenting with a recurrent aTTP episode (exacerbation or delayed relapse), with a clinically relevant rate of 12.7% versus 38.4% (p<0.001),
    - the absence of demonstration of an effect of CABLIVI compared to placebo, both combined with plasma exchanges and immunosuppression, on other clinically relevant endpoints, such as visceral pain or mortality,
    - an acceptable safety profile, characterised by epistaxis, gingival bleeding, contusion and haematuria, with experience of use limited to the duration of the phase 3 study, i.e. 65 days,
- new data provided based on an analysis of the CNR-MAT registry and the PMSI, including methodological biases and not further supporting the efficacy of CABLIVI (caplacizumab) on clinically relevant endpoints, such as visceral pain, mortality or relapses,
- persistent uncertainties with respect to the long-term safety of CABLIVI (caplacizumab) in adults,
- the available data does not enable the clinical relevance of CABLIVI (caplacizumab) to be fully evaluated. In particular, it does not enable identification of a typology of patients who would most benefit from treatment with CABLIVI (caplacizumab),
- the seriousness of the disease and its rarity,

the Committee considers that **CABLIVI (caplacizumab), in conjunction with standard treatment for the aTTP episode, including plasma exchange combined with immunosuppression, provides a minor clinical added value (CAV IV) compared to standard treatment.**