HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
5 JANUARY 2022

The legally binding text is the original French opinion version

selumetinib
KOSELUGO 10 mg hard capsules
KOSELUGO 25 mg hard capsules

First assessment

Key points

Favourable opinion for reimbursement in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above.

What therapeutic improvement?

Therapeutic improvement in the management of the disease

Role in the care pathway?

The treatment of neurofibromatosis type 1 (NF1) is based on specific monitoring with the aim of detecting complications at an early stage and treating them as they occur. There are no curative treatments.

The current management of plexiform neurofibromas (PN) in paediatric patients consists of either monitoring if they are asymptomatic or a multidisciplinary team meeting assessment of a surgical indication in the event of significant tumour progression and/or the development of symptoms that can be attributed to the PN.

Early excision (during childhood) is recommended by certain experts in order to limit the functional and aesthetic impact, especially where this appears to be aesthetically reasonable and complete excision is possible. Plexiform neurofibromas can recur over time and it is sometimes necessary to perform one or more procedures after the initial surgery.

For some patients, complete excision of PNs is not possible due to their proximity to vital organs or their invasive nature. This surgery can cause bleeding complications, particularly in the event of a PN with bulky, hypervascularised lesions.

Following total or partial excision, complications occur in 18% of patients (nerve paralysis, pain, speech problems). PN recurs in 55% of patients.

Allogeneic transplantation remains indicated in exceptional cases in plexiform neurofibroma of the face for which there is no surgical alternative (total functional destruction of the orbicularis oris muscle, in particular).

Concerning medicinal treatments, KOSELUGO (selumetinib) is the only medicinal product with an MA in the treatment of inoperable plexiform neurofibromas. New therapeutic options are currently the subject of clinical studies in the treatment of plexiform neurofibromas (e.g. mirdametinib and cabozantinib).

Role of KOSELUGO (selumetinib) in the care pathway:

KOSELUGO (selumetinib) is the first representative of the selective MEK (mitogen activated protein kinase) 1 and 2 inhibitors class, and the only medicinal product that currently has an MA as monotherapy in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above (conditional MA). Based on the results of a non-comparative, phase 2 study suggesting an objective response rate of 66%, it is an interesting treatment option for the management of patients with symptomatic inoperable plexiform neurofibromas (PN) in a context of an unmet medical need.

However, the data supporting its efficacy is marked by methodological weaknesses (data obtained from a non-comparative study, a primary endpoint that is not very robust, non-ranking of nonetheless interesting secondary endpoints). In addition, the long-term follow-up data is still limited (only 2 years of data available) and its safety profile is marked by adverse events, particularly gastrointestinal and cutaneous, and the need for regular monitoring, particularly of cardiac and ocular function.

As regards the administration methods and the pharmaceutical formulation proposed, the Committee highlights that the administration conditions for this medicinal product can be restrictive since they require patients to fast for 2 hours before and 1 hour after intake of the medicinal product (see sections 4.5 and 5.2 of the SPC). The Committee points out that the need to be able to swallow the hard capsules, which cannot be opened, may be a limiting factor in the prescription of KOSELUGO (selumetinib) depending on the child's age. Therefore, considering the choking risk due to difficulty swallowing whole tablets (which cannot be opened) in certain children, particularly those aged < 6 years, the Committee reiterates that selumetinib should not be administered to patients who are unable or unwilling to swallow the capsule whole (see section 4.2 of the SPC). It is particularly interested in the rapid development of a pharmaceutical form suitable for children aged under 6 years (granule formulation under development, scheduled to be submitted to the EMA in 2024).

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Neurofibromatosis type 1 (NF1) is a serious, life-threatening disease.

◗ KOSELUGO (selumetinib) is a curative medicinal product for inoperable plexiform neurofibromas (PN) associated with neurofibromatosis type 1. However, its effect is suspensive. There is currently no curative treatment for this disease.

◗ Its efficacy/adverse effects ratio is high.

◗ There are no alternatives in the treatment of symptomatic inoperable plexiform neurofibromas (PN) associated with neurofibromatosis type 1.

◗ KOSELUGO (selumetinib) is a treatment for symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 aged 3 years and above.

Public health impact

Considering:

- the seriousness of neurofibromatosis type 1 and its prevalence (estimated to be between 1/3,000 and 1/6,000 worldwide),
- the unmet medical need for symptomatic and inoperable forms,
- the partial response to the identified need due to the expected additional impact on morbidity in view of data suggesting a reduction in tumour volume via the confirmed partial response rate observed in 66% of patients in the phase 2 SPRINT study stratum 1, but considering the methodological limitations of this data in the absence of robust data on quality of life supporting an improvement in quality of life in treated patients,
- administration difficulties in children aged under 6 years due to the pharmaceutical form proposed: a hard capsule that cannot be opened,
- the absence of any demonstrated impact on the organisation of care,

KOSELUGO (selumetinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of KOSELUGO (selumetinib) is substantial in the MA indication.

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 MA indication and at the MA dosages.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- **data suggesting an objective response rate of 66%; $CI_{95\%}$ = [51.2 - 78.8] in patients treated with selumetinib in the non-comparative, phase 2 SPRINT study stratum 1 (confirmed partial response without an observed complete response, reflecting only a reduction in tumour volume),**
- **the unmet medical need in the treatment of symptomatic inoperable plexiform neurofibromas,**

But:

- **the impossibility of quantifying the specific effect of treatment with selumetinib due to the non-comparative methodology of the phase 2 SPRINT study stratum 1, despite the fact that a comparative study could have been performed,**
- **the not very robust primary endpoint and the absence of ranking of secondary endpoints, which are nonetheless major in NF1 (reduction of symptoms or pain, improvement in quality of life).**
- **uncertainties concerning the long-term efficacy and safety, pending long-term data from the phase 2 SPRINT study, stratum 1,**
- **the safety profile of KOSELUGO (selumetinib) marked by adverse events, in particular gastrointestinal and cutaneous, and the need for regular monitoring, particularly of cardiac and ocular function,**
- **the non-availability to date of a pharmaceutical formulation suitable for children, particularly under the age of 6 years, which is regrettable, especially given that an important potential risk of choking due to difficulty swallowing capsules, is included in the RMP,**
- **available exploratory data concerning quality of life not enabling a conclusion to be reached for this endpoint,**

the Committee considers that KOSELUGO (selumetinib) provides a minor clinical added value (CAV IV) in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 aged 3 years and above.