HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
9 JULY 2020

The legally binding text is the original French opinion version

larotrectinib
VITRAKVI 25 and 100 mg hard capsules
VITRAKVI 20 mg/ml oral solution

First assessment

Key points

Favourable opinion for reimbursement only in the treatment of paediatric patients with refractory or relapsed, locally advanced or metastatic infantile fibrosarcoma or another soft tissue sarcoma, with NTRK (Neurotrophic Tyrosine Receptor Kinase) gene fusion.

Maintenance of this opinion is subject to submission of comparative data for VITRAKVI (larotrectinib) versus the standard of care in these patients within a maximum period of 12 months, as well as the implementation of an exhaustive registry identifying all children treated with VITRAKVI in France.

Unfavourable opinion for reimbursement in the other paediatric indications included in the MA and in adults with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion:
- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- who have no satisfactory treatment options.

What therapeutic improvement?

No clinical added value, on the basis of currently available data, in the treatment of paediatric patients with refractory or relapsed, locally advanced or metastatic infantile fibrosarcoma or another soft tissue sarcoma, with NTRK gene fusion.

Role in the care pathway?

Solid tumours with NTRK gene fusion represent a heterogeneous group of tumours, in both adults and children. At present, the frequency of fusion is not precisely known. Overall, this frequency is low (0.5% to 1%) in common cancers (e.g. lung, prostate, colon and breast cancers) and in CNS tumours, whereas it is high (> 80%) for certain rare cancers, for example in adults with salivary gland cancer of subtype MASC - Mammary Analogue Secretory Carcinoma, secretory breast cancer, and, in children, infantile fibrosarcoma.

Currently, the prognostic value of NTRK 1, 2 or 3 fusion in solid cancers is not known and the French national health insurance system funds only IHC-based detection tests, not NGS or RT-PCR tests. The molecular biology platforms of university hospitals and cancer centres perform the test on demand. In some rare tumours, the detection of this abnormality is an integral part of the diagnosis, particularly for infantile fibrosarcoma.

Role of the medicinal product in the care pathway

In paediatrics, despite the low level of evidence of the data supplied and pending new efficacy and safety data, the Committee considers that VITRAKVI (larotrectinib), as monotherapy, is a treatment option for patients with refractory or relapsed, locally advanced or metastatic infantile fibrosarcoma or other paediatric soft tissue sarcomas, with NTRK gene fusion.

In view of the number of patients having received an objective response in a non-comparative phase I/II study and according to the experts, VITRAKVI (larotrectinib) could have a limited role in the paediatric management of:

- infantile fibrosarcoma with NTRK gene fusion in the event of failure of vincristine-actinomycin chemotherapy (the reference treatment for several decades) and the impossibility of non-mutilating surgery, to avoid exposure to intense chemotherapy, and for exceptional refractory or relapsed metastatic forms;
- other paediatric soft tissue sarcomas with NTRK gene fusion following failure of standard therapies, for refractory or relapsed tumours.

It is necessary to indicate that in a context in which no comparative data are available to guarantee the solidity of the conclusion with respect to the effect of treatment with VITRAKVI (larotrectinib), the introduction of this medicinal product into the treatment strategy is accompanied by a higher risk than for medicinal products for which the efficacy is based on a comparison conducted with control of the risk of wrongly concluding that the treatment is effective (two-tailed alpha risk conventionally accepted to be 5%).

The Committee recommends that the choice of treatment should be made in the context of the proposal made following a multidisciplinary review meeting, in order to supervise the limited role of VITRAKVI (larotrectinib) in the therapeutic strategy.

In the other situations included within the broad scope of the MA and in view of available data based on three phase I, I/II and II non-comparative proof of concept studies, which are insufficient to support the clinical benefit of VITRAKVI (larotrectinib), in a context in which the prognostic value of the presence of NTRK gene fusion is not known, the Committee considers that VITRAKVI (larotrectinib) has no role in the therapeutic strategy, despite the medical need that may be unmet, particularly in last-resort situations.

COMMITTEE'S CONCLUSIONS

Clinical benefit

In paediatrics

◗ Advanced or metastatic solid tumours, all locations combined, are life-threatening, with a variability depending on location and histology. The natural course of solid cancers with NTRK gene fusion has not been characterised and the prognostic value of NTRK gene fusion in solid cancers is not known in clinical practice. In the event of surgical resection resulting in severe morbidity, the quality of life of patients is significantly affected. The frequency of NTRK gene fusion is highly variable depending on the tumour location and is particularly high for infantile fibrosarcoma (≥ 80%).

◗ This is a specific curative cancer treatment.

◗ The efficacy/adverse effects ratio of VITRAKVI (larotrectinib) in paediatric patients has not been adequately established due to the weakness of demonstration of short-term efficacy (non-comparative phase I/II study, small population, fragmented efficacy data, little follow-up in terms of efficacy and tolerance) and in the absence of comparative data, at least with external control scheduled in advance (see Section 07.6 Summary and Discussion). However, the exploratory data in this study primarily concern three types of tumours, including infantile fibrosarcoma and soft tissue sarcomas, for which high response rates were suggested, although with limited population sizes and a short follow-up period.

◗ There are no medicinal alternatives with an MA targeting NTRK gene fusion. In infantile fibrosarcoma and in the other soft tissue sarcomas, several chemotherapy lines can be proposed. Once all the available options have been exhausted, there are no other alternatives, apart from supportive care.

◗ As the dossier currently stands, despite the low level of evidence of the data in the infantile fibrosarcoma and other soft tissue sarcomas subgroups, VITRAKVI may have a role in the therapeutic strategy in situations limited to refractory or relapsed, locally advanced or metastatic infantile fibrosarcoma or other soft tissue sarcomas, with NTRK gene fusion.
In other situations, VITRAKVI (larotrectinib) has no role in the therapeutic strategy (see Section 08 Role of the therapeutic strategy).

Public health impact
Despite:
- the seriousness of the diseases concerned,
- the low prevalence of solid tumours with NTRK gene fusion, with, in particular, a very high frequency of NTRK gene fusion in infantile fibrosarcoma,
- the medical need that is inadequately met or unmet depending on the situation,

and considering:
- the partial response that VITRAKVI may provide, pending additional data, in refractory or relapsed, locally advanced or metastatic fibrosarcoma and other paediatric soft tissue sarcomas with NTRK gene fusion,
- the lack of response to the identified need in other clinical situations in view of the preliminary, non-comparative data, the fragmented quality of life data, and uncertainties in terms of long-term safety, in particular neurological development including cognitive functions,
- the transposability of the results, which is not guaranteed, particularly in view of the inclusion criteria for infantile fibrosarcoma allowing inclusion from the time of diagnosis, without consideration of eligibility for the reference vincristine-actinomycin chemotherapy in the SCOUT study. (see Section 07.7 Summary and discussion),
- the impact on the organisation of care, with the need to implement one or more diagnostic tests with an NTRK gene fusion detection strategy as part of routine clinical management,

VITRAKVI (larotrectinib) is unlikely to have an additional impact on public health in paediatrics.

Considering all these elements, the Committee deems that the clinical benefit of VITRAKVI (larotrectinib) is:
- **<u>moderate</u> only in refractory or relapsed, locally advanced or metastatic infantile fibrosarcoma and other paediatric soft tissue sarcomas with NTRK gene fusion;**
- **<u>insufficient</u> in the other paediatric situations to justify public funding cover.**

The Committee makes maintenance of the moderate clinical benefit conditional on the reevaluation of VITRAKVI (larotrectinib) on the basis of (see 011 Committee recommendations):
- **comparative data for VITRAKVI versus the standard of care for these patients, to be submitted within a maximum period of 12 months,**
- **and the implementation of an exhaustive registry identifying all children treated with VITRAKVI in France.**

In adults

◗ Locally advanced or metastatic solid tumours, all locations combined, are life-threatening, with a variability depending on location, histology and age, in particular. The 5-year survival ranges from 4% to 98% depending on the type of cancer. The natural course of solid cancers with NTRK gene fusion has not been characterised and the prognostic value of NTRK gene fusion in solid cancers is not known in clinical practice.

◗ This is a specific curative cancer treatment.

◗ In all advanced solid tumours displaying NTRK gene fusion (including primary CNS tumours) and in situations for which surgical resection would involve a risk of severe morbidity, all the data submitted do not enable confirmation of the efficacy of larotrectinib, by targeting NTRK gene fusions, independently of tumour site. The efficacy/adverse effects ratio of VITRAKVI (larotrectinib) has not been adequately established considering the low level of evidence of data founded on two non-comparative phase I and II studies, for which inclusions are ongoing, that do not enable the clinical benefit to be determined given uncertainties related, in particular, to (see Section 07.6 Summary and Discussion):
- the absence of homogeneity of the benefit, irrespective of solid tumour;
- preliminary data supporting a heterogeneous indication in terms of tumour location, prognosis specific to each tumour and treatment lines;
- the prognostic value of NTRK gene fusion, which is not documented;

and despite the seriousness of the clinical situations concerned.
◗ There are no medicinal alternatives with an MA targeting NTRK gene fusion. Once all the available options have been exhausted, there are no other alternatives, apart from supportive care.

◗ As the dossier currently stands, given the low level of evidence of the data, in a context in which the prognostic value of the presence of NTRK gene fusion is not known, VITRAKVI (larotrectinib) has no role in the care pathway in adults (see Section 08 Role in the care pathway).

<u>Public health impact</u>
Despite:
- the seriousness of the disease,
- the low prevalence or incidence of solid tumours with NTRK gene fusion,
- the medical need that is inadequately met or unmet depending on the situation,

and considering:
- the lack of response to the identified need in view of the preliminary, non-comparative data and the fragmented quality of life data,
- the non-guaranteed transposability of the results (see Section 07.7 Summary and discussion),
- the impact on the organisation of care, with the need to implement one or more diagnostic tests with an NTRK gene fusion detection strategy as part of routine clinical management for

a high number of solid cancers (in particular, among all metastatic solid cancers, 180,000 new cases per year according to the French National Cancer Institute (INCa)[1]), which has not currently been optimally established.

VITRAKVI (larotrectinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of VITRAKVI (larotrectinib) is <u>insufficient</u> in adults in the marketing authorisation indication to justify its funding by the French national health insurance system.

Clinical Added Value

In paediatrics: in refractory or relapsed, locally advanced or metastatic infantile fibrosarcoma and other paediatric soft tissue sarcomas with NTRK gene fusion

Considering:

- **the data from the non-comparative phase I/II SCOUT study mainly concerning three types of tumours, including infantile fibrosarcoma (N=34) and other soft tissue sarcomas (N=21), suggesting high objective response rates under treatment with larotrectinib in these small subpopulations, with a short follow-up period, but,**
- **uncertainties, particularly related to the absence of comparative data versus the standard of care,**
- **the absence of data on criteria other than response rate, in particular overall survival and quality of life,**

and despite the substantial medical need in these rare cancers,
the Committee considers that VITRAKVI (larotrectinib), as monotherapy, provides no clinical added value (<u>CAV V</u>) in the treatment strategy for paediatric patients with refractory or relapsed, locally advanced or metastatic infantile fibrosarcoma or another soft tissue sarcoma, with NTRK gene fusion.

In the other paediatric indications and in adults

Not applicable.

[1] Report on selective TRK inhibitors submitted to the HAS in November 2019