HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
15 DECEMBER 2021

The legally binding text is the original French opinion version

fedratinib
INREBIC 100 mg hard capsules

First assessment

Key points

Favourable opinion for reimbursement in the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

Allogeneic haematopoietic stem cell transplantation (HSCT) is the only curative treatment usually indicated in patients with relatively advanced, intermediate or high-risk disease, but only the minority of patients are eligible for transplant (due to their age and/or general health status and the need to have a compatible donor available). For patients not eligible for transplant, treatment depends on the myelofibrosis risk level (IPSS score) and the patient's symptoms. The objective is to improve the symptoms, whether they are constitutional or directly associated with splenomegaly and/or haematopoiesis abnormalities.

Apart from allogeneic transplantation, which concerns very few patients, there are no treatments available capable of inducing a constant and definitive regression of myelofibrosis. Treatment is primarily palliative, slowing down the progression of fibrosis or reducing splenomegaly and inflammatory symptoms, or compensating for the consequences of cytopenia. The medicinal products used are hydroxyurea, interferon alpha, corticosteroids, IMiD (lenalidomide, revlimid), and transfusions.

Hydroxyurea is used in routine practice based on a benefit that was inadequately established in old studies. Its use has been replaced by that of JAK inhibitors.

JAKAVI (ruxolitinib) was the first JAK inhibitor to have obtained an MA in the treatment of myelofibrosis. Its efficacy in the treatment of patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis has been established for reducing spleen volume and the resulting symptoms.

In the event of failure or intolerance to ruxolitinib, no second-line therapy previously had an MA or was recommended in the treatment of splenomegaly and symptoms associated with myelofibrosis.

Role of INREBIC (fedratinib) in the care pathway:

INREBIC (fedratinib) is the second representative of the Janus Associated Kinase (JAK) inhibitor class indicated in the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are JAK inhibitor naïve or have been treated with ruxolitinib (the other JAK inhibitor currently available). Its efficacy has been established for spleen volume reduction.

In JAK inhibitor naïve patients, in the absence of comparative data, the role of INREBIC (fedratinib) compared to JAKAVI (ruxolitinib) cannot be determined.

In patients previously treated with ruxolitinib, INREBIC (fedratinib) is a treatment option but uncertainties remain concerning its contribution given the absence of a comparative approach and the non-consensual definition of ruxolitinib resistance.

Considering the risk of the development of Wernicke's encephalopathy (WE) identified during clinical studies with a dosage higher than that recommended (500 mg), the Committee highlights the importance of assessing then monitoring thiamine levels before initiating treatment with fedratinib then periodically during treatment. It also highlights that, as specified in the SPC, any change in mental status, confusion or memory impairment should raise concern for potential encephalopathy, including Wernicke's and prompt a full evaluation including a neurologic examination, assessment of thiamine levels and imaging (see sections 4.2 and 4.8 of the SPC).

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

In Janus Associated Kinase (JAK) inhibitor naïve patients

◗ Myelofibrosis is a serious disease that is life-threatening.

◗ The proprietary medicinal product INREBIC (fedratinib) is a symptomatic medicinal product.

◗ The efficacy/adverse effects ratio of INREBIC (fedratinib) is moderate given its demonstrated efficacy in terms of spleen volume reduction but its safety profile marked by haematological toxicity and a potential risk of the development of Wernicke's encephalopathy.

◗ There is a therapeutic alternative (ruxolitinib).

◗ INREBIC (fedratinib) is a treatment for disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are JAK inhibitor naïve. Its role compared to JAKAVI (ruxolitinib) cannot be determined in the absence of comparative data.

Public health impact

Considering:

- the seriousness of myelofibrosis and its low incidence,
- the partially met medical need,
- the lack of response to the identified need due to:
  - the absence of an additional impact of INREBIC (fedratinib) demonstrated on morbidity and mortality or quality of life compared to JAKAVI (ruxolitinib) but considering the concomitant development with the latter, making direct comparison impossible,
- the absence of any demonstrated impact on the organisation of care,

INREBIC (fedratinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of INREBIC (fedratinib) is moderate in the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve.

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 treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve and at the MA dosages.

◗ **Recommended reimbursement rate: 30%**

In patients who have been treated with ruxolitinib

◗ Myelofibrosis is a serious disease that is life-threatening.

◗ The proprietary medicinal product INREBIC (fedratinib) is a symptomatic medicinal product.

◗ Its efficacy/adverse effects ratio is moderate given a suggested efficacy in a non-comparative study in terms of spleen volume reduction and its safety profile marked by haematological toxicity and a potential risk of the development of Wernicke's encephalopathy.

◗ There are therapeutic alternatives although their efficacy data is limited.

◗ INREBIC (fedratinib) is a treatment option in a context of a substantial medical need in patients resistant or intolerant to treatment with ruxolitinib.

Public health impact

Considering:

- the seriousness of myelofibrosis and its low incidence,
- the partially met medical need,
- the lack of response to the identified need due to:
  - the lack of any demonstrated additional impact on morbidity and mortality or on quality of life due to the non-comparative methodology of the JAKARTA-2 study,
- the absence of any demonstrated impact on the organisation of care,

INREBIC (fedratinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of INREBIC (fedratinib) is moderate in the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib.

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 indications/in the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib, and at the MA dosages.

◗ **Recommended reimbursement rate: 30%**

Clinical Added Value

In JAK inhibitor naïve patients

Considering:

- **demonstration of the superiority of INREBIC (fedratinib) in comparison with placebo in terms of spleen response rate ($SR_{35\%}$) with an absolute difference of 35.4% in favour of fedratinib 400 mg ($p < 0.0001$; $CI_{97.5\%}$ [24.2; 46.7]),**

But:

- **the absence of demonstration of an improvement in overall survival or progression-free survival,**
- **available exploratory data concerning quality of life not enabling a conclusion to be reached for this endpoint,**
- **the safety profile of INREBIC (fedratinib) marked by gastrointestinal and haematological (anaemia, thrombocytopenia) adverse events and the occurrence of potential serious cases of Wernicke's encephalopathy during studies, although at a dosage higher than that recommended in the indication,**
- **the lack of comparative data versus JAKAVI (ruxolitinib, clinically relevant comparator) but taking into account the concomitant development making the implementation of such a study impossible,**

the Committee considers that INREBIC (fedratinib) provides no clinical added value (CAV V) in the current care pathway including JAKAVI (ruxolitinib) for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are <u>JAK inhibitor naïve</u>.

In patients who have been treated with ruxolitinib

Considering:

- **a suggested spleen volume reduction ($SR_{35\%}$) in 48.2% ($CI_{95\%}$ = [37.1; 59.4]) in patients previously treated with ruxolitinib and treated with fedratinib in the JAKARTA-2 study,**

But:

- **the impossibility of quantifying the specific effect of treatment with fedratinib due to the non-comparative methodology of the JAKARTA-2 study,**
- **the safety profile of INREBIC (fedratinib) marked by gastrointestinal and haematological (anaemia, thrombocytopenia) adverse events and the occurrence of potential serious cases of Wernicke's encephalopathy during studies, although at a dosage higher than that recommended in the indication,**
- **the available exploratory data on quality of life,**

the Committee considers that INREBIC (fedratinib) provides no clinical added value (CAV V) in the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis <u>who have been treated with ruxolitinib</u>.