HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

16 DECEMBER 2020

The legally binding text is the original French opinion version

This opinion was the subject of an amendment, presented at the Committee's session of 20 January 2021, in order to correct a drafting error.

nintedanib

OFEV 100 mg and 150 mg soft capsules

New indication

Key points

Favourable opinion for reimbursement in the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

What therapeutic improvement?

Therapeutic improvement in the management of the disease.

Role in the care pathway?

The therapeutic management of systemic sclerosis (SSc) is difficult due to its clinical heterogeneity, the involvement of several organs and the absence of global treatment acting simultaneously on each of the different pathogenic mechanisms. In a multidisciplinary approach, the treatment of organ involvement is the primary objective and depends on the type and severity of this involvement.

Questioning seeks to identify any occupational exposure to silica or solvents, leading to specification of risk factors and performance of an occupational investigation. It is also necessary to identify any factors liable to exacerbate vascular disease (hammering, vibrations), as well as exposure to tobacco smoke.

The diagnosis should be considered in the event of combination of several criteria defined in the ACR/EULAR classification: Raynaud's phenomenon (present in more than 95% of cases), cutaneous sclerosis, trophic disorders, such as fingertip ulcers or pitting scars, calcinosis and joint or muscle and tendon involvement.

Assessment should be routinely conducted to identify the presence of any pulmonary involvement. If pulmonary involvement is detected, regular monitoring should be put in place to measure the evolution of interstitial lung disease (ILD).

The severity of ILD is measured by assessing dyspnoea, transcutaneous oxygen saturation, forced vital capacity (FVC) and total lung capacity, carbon monoxide diffusing capacity (DLCO), chest high resolution computed tomography (HRCT) scan data (extent and characteristics of lung lesions).

The French national diagnostic and care protocol (PNDS) recommends treating patients with progressive ILD (10% loss of FVC or ≥ 200 mL and/or 15% of DLCO) or ILD that is severe from the outset.

Mycophenolate Mofetil (MMF) is recommended as first-line treatment, and cyclophosphamide IV as second-line treatment or as first-line treatment in fast-progressing forms or those with a poor prognosis. Rituximab is reserved for third-line treatment.

Each treatment line should be reassessed after 6 months of treatment on the basis of clinical data (NYHA functional class, 6 min walking test) and pulmonary function tests. A HRCT scan should be performed at the end of the treatment sequence and in the event of clinical worsening.

In the event of stabilisation or improvement of clinical condition, respiratory function tests or scan results, immunosuppressant therapy is continued for at least 2 years (there is a lack of published data beyond this period). Cyclophosphamide IV can be continued for 12 months and is then followed by azathioprine or MMF.

In ILD forms with severe respiratory failure despite the previously cited treatments, and in the absence of other severe organ involvement, lung transplantation may be considered.

Role of the medicinal product in the care pathway

OFEV can be used alone or in combination with immunomodulators and/or oral corticosteroids in patients with a clinical and radiological diagnosis of SSc-ILD.

It should be highlighted that the efficacy and safety data were only obtained in patients with a pulmonary fibrosis extension of more than 10%, confirmed with the following respiratory function criteria: FVC ≥ 40% and DLCO ≥ 30%.

Special recommendations

Due to the complexity of diagnosing and managing these diseases, the Committee recommends that the decision to initiate OFEV (nintedanib) treatment be discussed during a multidisciplinary team (MDT) meeting and that the decision be tracked, then submitted and explained to the patient.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Interstitial lung diseases (ILD) are defined as a diffuse, often fibrosing inflammatory process that leads to non-specific clinical symptoms, dominated by dyspnoea and cough, and radiological signs of diffuse interstitial lung disease that gradually progresses towards restrictive chronic respiratory failure and the patient's death.
ILD is one of the most severe complications of systemic sclerosis (SSc-ILD). The clinical manifestations associated with SSc-ILD, which are initially minimal or non-existent, usually progress to severe lung disease, leading to irreversible respiratory failure and the patient's death.

◗ OFEV (nintedanib) is a symptomatic treatment.

◗ Considering:
- a moderate size effect of OFEV (nintedanib) versus placebo in terms of annual rate of decline in forced vital capacity (FVC) (primary endpoint which is an intermediate endpoint but was judged to be clinically relevant by the Committee);
- the absence of robust data in terms of quality of life and survival, criteria that are very relevant in this disease;
- the acceptable safety profile, marked primarily by diarrhoea, but;
- the very short follow-up for assessment of its efficacy and safety in this indication;

its efficacy/adverse effects ratio is moderate.

◗ There are no alternatives with an MA in the treatment of SSc-ILD. Nevertheless, the French national diagnostic and care protocol (PNDS) recommends the off-label use of mycophenolate mofetil, cyclophosphamide IV or rituximab, depending on the treatment line. In certain very specific cases, treatment by autologous haematopoietic stem cell transplantation or lung transplant may be considered.

◗ This proprietary medicinal product can be used alone or in combination with immunomodulators and/or oral corticosteroids in patients with a confirmed clinical and radiological diagnosis of SSc-ILD (see 9 "Role in the care pathway" of the French opinion version).

◗ <u>Public health impact</u>:
Considering:
- the chronic, rare and serious nature of systemic sclerosis associated interstitial lung disease (SSc-ILD),
- the medical need partially met by current management,
- the partial response to the identified medical need in view of a moderate efficacy on morbidity and the absence of demonstration on mortality in a population for which the transposability cannot be guaranteed due to the difficulty identifying patients with SSc-ILD,
- the absence of robust quality of life data,
- the absence of any demonstrated impact on the organisation of care,

OFEV (nintedanib) is unlikely to have an impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of OFEV (nintedanib) is moderate in the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

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 systemic sclerosis associated interstitial lung disease and at the MA dosages.

- **Recommended reimbursement rate: 30%**

Clinical Added Value

Considering:

- **demonstration in a phase 3, randomised, double-blind study of the superiority of OFEV (nintedanib) compared to placebo but with a moderate effect size on an intermediate but clinically relevant primary endpoint (difference of 40.95 ml/year between the two groups for the annual rate of decline in forced vital capacity);**
- **its satisfactory safety, marked primarily by diarrhoea, and experience of its use in other interstitial lung diseases;**
- **the medical need in this rare disease in the absence of a therapeutic alternative with an MA;**

but the absence of:

- **robust data in terms of survival of treated patients;**
- **robust data in terms of quality of life in these diseases that significantly impact this;**
- **long-term data in diseases that, nonetheless, progress slowly;**

the Committee considers that OFEV provides a minor clinical added value (CAV IV) in the current care pathway for the treatment of patients with systemic sclerosis associated interstitial lung disease (SSc-ILD).