17 April 2020
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Ofev (Nintedanib)

Treatment of systemic sclerosis

EU/3/16/1724

Sponsor: Boehringer Ingelheim International GmbH

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substances at the time of orphan designation	Nintedanib
Other names	Nintedanib, Ofev
International Non-Proprietary Name	Nintedanib
Tradename	Ofev
orphan condition	Treatment of systemic sclerosis
Sponsor's details:	Boehringer Ingelheim International GmbH Binger Strasse 173 55216 Ingelheim Am Rhein Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Boehringer Ingelheim International GmbH
COMP opinion date	13 July 2016
EC decision date	29 August 2016
EC registration number	EU/3/16/1724
Marketing authorisation type II variation procedural history	
Rapporteur / Co-rapporteur	Peter Kiely / Ewa Balkowiec Iskra
Applicant	Boehringer Ingelheim International GmbH
Application submission date	27 August 2019
Procedure start date	14 September 2019
Procedure number	EMEA/H/C/003821/II/0026
Invented name	Ofev
Proposed therapeutic indication	Ofev is indicated in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF). Further information on Ofev can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/ Ofev
CHMP opinion date	27 February 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Martin Mozina / Eva Malikova
Sponsor's report submission date	15 March 2019
COMP discussion	17-19 March 2020
COMP opinion date	19 March 2020

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2016 designation was based on the following grounds:

The sponsor Boehringer Ingelheim International GmbH submitted on 19 May 2016 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing nintedanib for treatment of systemic sclerosis (hereinafter referred to as "the condition").

The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

• the intention to treat the condition with the medicinal product containing nintedanib was considered justified based on in vivo preclinical data demonstrating antifibrotic effects;

• the condition is chronically debilitating and life-threatening due to the deposition of collagen in the skin and in internal organs such as kidneys, heart, lungs and gastrointestinal tract, leading to severe complications such as pulmonary hypertension, progressive dysphagia, sclerodermal renal crisis and cardiac failure;

• the condition was estimated to be affecting less than 3.5 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing nintedanib will be of significant benefit to those affected by the condition. The

sponsor has provided preclinical data that demonstrate an antifibrotic effect of the proposed product which is directly associated with the condition and not targeted by the currently authorised treatment.

The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing nintedanib as an orphan medicinal product for the orphan indication: treatment of systemic sclerosis.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The approved therapeutic indication "Treatment of Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)" falls within the scope of the designated orphan condition "Treatment of systemic sclerosis".

Systemic sclerosis (SSc) is a generalized disorder of connective tissue characterized by thickening and fibrosis of the skin (scleroderma) and by distinctive forms of involvement of internal organs, notably the heart, lungs, kidneys and gastrointestinal tract. Vascular injury dominates the clinical manifestations in all forms of the disorder. The aetiology and pathogenesis are unknown.

SSc is rapidly progressive. Excessive collagen deposition, with scleroderma and widespread microvascular damage, results in the occurrence of Raynaud's phenomenon, the episodic vasospasms of the peripheral arteries (80-95% of patients) and typically precedes the onset of systemic disease by several years.

SSc is more common in women and can be divided into limited cutaneous SSc and diffuse cutaneous SSc. Limited cutaneous SSc primarily affects the hands, arms and face and is associated with Raynaud's phenomenon. Interstitial lung disease (ILD) is common in adult patients with SSc. Up to 90% of adult patients develop abnormalities on high resolution computer tomography (HRCT) and 40-75% of patients will show lung function abnormalities.

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP. Please see EPAR.

Chronically debilitating and/or life-threatening nature

There have been no changes in the seriousness of the condition since the time of orphan designation.

The condition is chronically debilitating due to the deposition of collagen in the skin and, less commonly, in the kidneys, heart, lungs and stomach. This deposition presents in two forms: diffuse scleroderma which affects the skin as well as the heart, lungs, gastrointestinal tract and kidneys and localized scleroderma which affects the skin of the face, neck, elbows and knees and late in the disease causes isolated pulmonary hypertension. Common complications seen with the diffuse form are pulmonary hypertension, reflux esophagitis and dysphagia, as well as the appearance of sclerodermal renal crisis. Interstitial lung disease (ILD) is also common in systemic sclerosis (SSc) patients. Patients with SSc suffer from a significant impairment of health-related quality of life when compared to the general population. Pulmonary involvement (interstitial lung disease or pulmonary hypertension) is currently the leading causes of death (ILD accounting for 33% of deaths and PAH for 28%).

Number of people affected or at risk

The sponsor performed an extensive review of the literature on the prevalence of the condition. Specific databases for the condition were not retrieved that report the prevalence of the condition.

A number of studies were retrieved that had assessed the prevalence rate of SSc in the general population. Estimates vary across studies, from 9.9 per 100,000 in Norway for the year 2009 [R16-1346] to 34.8 per 100 000 in Sardinia, Italy in 2012. Such variation may be partly due to differences in the design and methods used to calculate these estimates, but also explained by differences in the diagnostic criteria for SSc used in the different studies. As an example, the most recent estimates of

SSc prevalence reported for Sweden in 2010 are 23.5 per 100,000 and 30.5 per 100,000, using respectively, the 1980 ACR diagnostic criteria and the 2012 proposed ACR/EULAR criteria

According to the literature search performed, the maximum prevalence rate for SSc is estimated to be below 3.5 per 10,000 persons in the EU, which is in line with previous designations.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Bosentan (Tracleer), an endothelin receptor antagonist, is authorised in the EU for primary pulmonary arterial hypertension (PAH) and PAH secondary to SSc without significant interstitial pulmonary disease to improve exercise capacity and symptoms in patients with WHO functional class II. Bosentan is also indicated to reduce the number of new digital ulcers in patients with SSc and ongoing digital ulcer disease (Tracleer). No other drugs are currently authorised in the EU for the treatment of SSc or SSc-related symptoms or sequelae.

International treatment recommendations, initiated by EULAR/EUSTAR, were updated in 2017 and they mention several drugs approved in other indications to treat SSc-related symptoms including immunosuppressive treatments, cyclophosphamide, methotrexate, and mycophenolate. These products are not specifically approved for SSc-ILD.

The use of immunosuppressive therapies, particularly cyclophosphamide (CYC) and mycophenylate mofetil (MMF) in SSc-ILD is based on the results of two pivotal clinical trials. The Scleroderma Lung Study I showed a 1% change in FVC with placebo and 2.6% in patients treated with CYC at 12 and 18 months, even though however no differences between groups were shown after 24 months of treatment. In the Scleroderma Lung Study II comparing CYC vs. MMF, the results showed that MMF was as effective and safer than CYC over a 24-month time period. Although this trial had a large dropout rate and lacked a placebo arm, MMF became part of the standard of care for SSc-ILD.

Significant benefit

The significant benefit of nintedanib in relation to Tracleer, authorized for PAH secondary to SSc without significant interstitial pulmonary disease, and to reduce the number of new digital ulcers in patients with SSc, is justified based on the different therapeutic indication, as OFEV targets SSc-ILD.

The significant benefit in patients with SSc-ILD was demonstrated in the pivotal trial at the basis of the marketing authorization, a single large Phase III trial (SENSCIS) on 580 patients, randomised 1:1 to receive nintedanib 150 mg/twice daily or placebo. Randomisation was stratified based on the antitopoisomerase antibody (ATA) status (positive or negative).

The primary endpoint was the annual rate of decline in forced vital capacity (FVC) in mL over 52 weeks. FVC is used as endpoints in most trials in ILDs and it has recently been reported that changes in quantitative fibrosis scoring of HRCT in the Scleroderma Lung Study II correlated with FVC and the transition dyspnoea index. The results of the SENCIS trial showed that the decline in the nintedanib group was 43.8% lower than in the placebo group, with an adjusted difference between the groups of 40.95 mL/year (95% CI 2.88, 79.01) and a p-value of 0.0350 (Table 1). The annual rate of decline in

FVC over 52 weeks was also investigated in subgroups defined by ATA status, gender, age, race, region, mycophenolate use at baseline, and SSc subtype. The analyses showed a consistent treatment effect across all subgroups.

In the subgroup of patients with mycophenolate use at baseline, the adjusted annual rate of decline in FVC over 52 weeks was -40.2 mL/year in the nintedanib group and -66.5 mL/year in the placebo group; the difference between the groups was 26.33 mL/year (95% CI -27.93, 80.59). In the subgroup without mycophenolate at baseline, the adjusted annual rate of decline in FVC over 52 weeks was -63.9 mL/year in the nintedanib group and -119.3 mL/year in the placebo group; the difference between the groups was 55.40 mL/year (95% CI 2.30, 108.50).

Table 1 Rate of decline in FVC [mL/yr] over 52 weeks in trial 1199.214 - TS

		Rate of decline over 52 weeks				Comparison vs. placebo				
				95% CI				95% CI		
Treatment	Number analysed	Adjusted rate[1]	SE	Lower	Upper	Adjusted difference[1]	SE	Lower	Upper	p-value
Placebo	288	-93.3	13.5	-120.0	-66.7					
Nintedanib 150 mg bid	287	-52.4	13.8	-79.6	-25.2	40.95	19.38	2.88	79.01	0.0350

1 Based on a random coefficient regression with fixed categorical effects of treatment, ATA status, gender, fixed continuous effects of time, baseline FVC [mL], age, height, and including treatment-by-time and baseline-by-time interactions. Random effect was included for patient specific intercept and time. Within-patient errors are modelled by an unstructured variance-covariance matrix. Inter-individual variability is modelled by a variance-components variance-covariance matrix.

Figure 1 below shows the curves of treatment and placebo separating after 12 weeks of treatment and continuing to diverge up to Week 52.

Figure 1 (from CHMP assessment report)

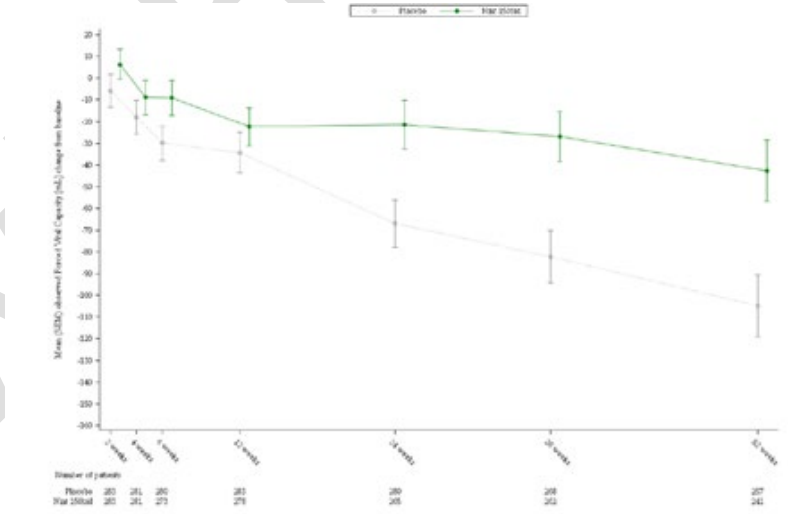

Figure 1 Mean (SEM) observed change from baseline in FVC [mL] over 52 weeks in trial 1199.214 - TS

As ILD is the major cause of mortality in SSc and decline in FVC has been associated with morbidity and mortality in patients with SSc, the effect of nintedanib was considered consistent with slowing progression of SSc-ILD, also supported by a scientific advisory group convened by the CHMP.

In summary, the only approved treatment for SSc targets PAH and digital ulcers associated with the disease, and there are no approved treatments which can modify or prevent progression of SSc-ILD and allow long term treatment in this chronic disease. Products that are not specifically authorized for the condition but used as standard of care, including immunosuppresants such as cyclophosphamide and mycophenolate, have shown limited benefits while carrying safety and tolerability issues that limit their use and, in case of cyclophosphamide, preclude chronic use.

In the SENCIS study, the treatment effect of nintedanib compared with placebo was observed irrespective of mycophenolate background treatment. Thus, nintedanib offers a viable treatment option for patients with SSc-ILD, with different mode of action and clinical improvement of lung function also on background of mycophenolate. As such the product is considered to be of significant benefit to those affected by the condition.

4. COMP position adopted on 19 March 2020

The COMP concluded that:

- the proposed therapeutic indication 'treatment of interstitial lung disease in systemic sclerosis' falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product: 'systemic sclerosis'.
- the prevalence of systemic sclerosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 3.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the deposition of collagen in the skin and in internal organs such as kidneys, heart, lungs and gastrointestinal tract, leading to severe complications such as pulmonary hypertension, interstitial lung disease, progressive dysphagia, sclerodermal renal crisis and cardiac failure;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Ofev may be of potential significant benefit to those affected by the orphan condition still holds. This is based on a pivotal clinical trial showing clinically relevant improvement of lung function measured over 52 weeks in patients treated with Ofev as compared to those taking placebo, on background treatment with mycophenolate. Ofev acts on the interstitial lung disease in systemic sclerosis, differently from the currently authorized products, which target other aspects of the condition. The committee considers that this constitutes a clinically relevant advantage for the patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Ofev, nintedanib, for treatment of systemic sclerosis (EU/3/16/1724) is not removed from the Community Register of Orphan Medicinal Products.