



COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

**PUBLIC SUMMARY OF
POSITIVE OPINION FOR ORPHAN DESIGNATION
OF**

**(S)-2-nitro-6-(4-trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b] [1,3] oxazine
for the treatment of tuberculosis**

On 29 November 2007, orphan designation (EU/3/07/513) was granted by the European Commission to Dr Ulrich Granzer, Germany, for (S)-2-nitro-6-(4-trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b] [1,3] oxazine for the treatment of tuberculosis.

What is tuberculosis?

Tuberculosis is an infection caused by a group of bacteria called *Mycobacterium*. It spreads from person-to-person by inhaling the infected airborne droplets generated by sneezing and coughing. The manifestation of the disease is variable and not all patients who are infected will develop the disease. Tuberculosis is characterised by fever, cough and breathing difficulties. The infection by the tuberculosis bacteria induces formation of granulomas, which are accumulations of large numbers of cells leading to chronic inflammatory lesions. Granulomas can develop in any tissue, but occur most often in the lungs (pulmonary tuberculosis). Tuberculosis can also affect the central nervous system (meningitis), lymphatic system, genitourinary system, bones and joints. Tuberculosis is a life-threatening condition.

What are the methods of treatment available?

The treatment of tuberculosis consists of the administration of a combination of antibiotics for long periods of time. Several medicinal products were authorised for the condition in the Community, at the time of submission of the application for orphan designation. Satisfactory argumentation has been submitted by the sponsor to justify the assumption that (S)-2-nitro-6-(4-trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b] [1,3] oxazine might be of potential significant benefit for the treatment of tuberculosis, mainly because it might improve the long-term outcome of the patients. The assumption of benefit will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

What is the estimated number of patients affected by the condition* ?

Based on the information provided by the sponsor and previous knowledge of the Committee, tuberculosis was considered to affect approximately 2 in 10,000 persons in the European Union, which, at the time of designation, corresponded to about 100,000 persons in total.

How is this medicinal product expected to act?

(S)-2-nitro-6-(4-trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b] [1,3] oxazine is considered as a potential anti-mycobacterial agent. It acts by inhibiting (blocking) the building of the

* Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed based on data from the European Union (EU 27), Norway, Iceland and Lichtenstein. This represents a population of 498,000,000 (Eurostat 2006). This estimate is based on available information and calculations presented by the sponsor at the time of the application.

mycobacterial cell wall components. The cell wall protects the microorganism from the outside and from external aggressions; its disruption can kill the microorganism.

What is the stage of development of this medicinal product?

The effects of (S)-2-nitro-6-(4-trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b] [1,3] oxazine have been evaluated in experimental models.

At the time of submission of the application for orphan designation, no clinical trials in patients with tuberculosis had been initiated.

(S)-2-nitro-6-(4-trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b] [1,3] oxazine had not been authorised anywhere worldwide for tuberculosis, at the time of submission. Orphan designation of the (S)-2-nitro-6-(4-trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b] [1,3] oxazine had been granted in the United States for the treatment of tuberculosis.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 10 October 2007 a positive opinion recommending the grant of the above-mentioned designation.

Opinions on orphan medicinal products designations are based on the following cumulative criteria: (i) the seriousness of the condition, (ii) the existence or not of alternative methods of diagnosis, prevention or treatment and (iii) either the rarity of the condition (considered to affect not more than five in ten thousand persons in the Community) or the insufficient return of development investments.

Designated orphan medicinal products are still investigational products which were considered for designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of the quality, safety and efficacy will be necessary before this product can be granted a marketing authorisation.

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**Translations of the active ingredient and indication in all EU languages
and Norwegian and Icelandic**

Language	Active Ingredient	Indication
English	(S)-2-nitro-6-(4-(trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine	Treatment of tuberculosis
Bulgarian	(S)-2- нитро -6-(4-(трифлуорометокси) бензилокси)-6,7-дихидро-5H-имидазо[2,1b][1,3]оксазин	Лечение на туберкулоза
Czech	(S)-2-nitro-6-(4-(trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin	Léčba tuberkulózy
Danish	(S)-2-nitro-6-(4-(trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin	Behandling af tuberkulose
Dutch	(S)-2-nitro-6-(4-(trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine	Behandeling van tuberculose
Estonian	(S)-2-nitro-6-(4-(trifluorometoksü)bensüüloksü)-6,7-dihüdro-5H-imidaso[2,1-b][1,3]oksasiin	Tuberkuloosi ravi
Finnish	(S)-2-nitro-6-(4-(trifluorometoksi)bentsyylloksi)-6,7-dihydro-5H-imidatso[2,1-b][1,3]oksatsiini	Tuberkuloosin hoito
French	(S)-2-nitro-6-(4-(trifluorométhy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine	Traitement de la tuberculose
German	(S)-2-Nitro-6-(4-(trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin	Behandlung der Tuberkulose
Greek	(S)-2-νιτρο-6-(4-(τριφθορομεθοξυ)-βενζυλοξυ)-6,7-διυδρο-5H-ιμιδαζο[2,1-b][1,3]οξάζινη	Θεραπεία της φυματίωσης
Hungarian	(S)-2-nitro-6-(4-(trifluor-metoxi)benziloxi)-6,7- dihidro-5H-imidazo[2,1-b][1,3]oxazin	Tuberculosis kezelése
Italian	(S)-2-nitro-6-(4-(trifluorometossi)benzilossi)-6,7-diidro-5H-imidazo[2,1-b][1,3]ossazina	Trattamento della tubercolosi
Latvian	(S)-2-nitro-6-(4-(trifluorometoksi)benziloksi)-6,7-dihidro-5H-imidazo[2,1-b][1,3]oksazīns	Tuberkulozes ārstēšana
Lithuanian	(S)-2-nitro-6-(4-(trifluorometoksi)benziloksi)-6,7-dihidro-5H-imidazo[2,1-b][1,3]oksazinas	Tuberkuliozės gydymas
Maltese	(S)-2-nitro-6-(4-(trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine	Kura tat-tuberkulosi
Polish	(S)-2-nitro-6-(4-(trifluorometoksy)benzyloksy)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oksazyna	Leczenie gruźlicy
Portuguese	(S)-2-nitro-6-(4-(trifluorometoxi)benziloxi)-6,7-dihidro-5H-imidazo[2,1-b][1,3]oxazina	Tratamento da tuberculose
Romanian	(S)-2-nitro-6-(4-(trifluorometoxi)benziloxi)-	Tratamentul tuberculozei

	6,7-dihidro-5H-imidazo[2,1-b][1,3]oxazínã	
Slovak	(S)-2-nitro-6-(4-(trifluórmetyoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazín	Liečba tuberkulózy
Slovenian	(S)-2-nitro-6-(4-(trifluorometoksi)benziloksi)-6,7-dihidro-5H-imidazo[2,1-b][1,3]oksazín	Zdravljenje tuberkuloze
Spanish	(S)-2-nitro-6-(4-(trifluorometoxi)benziloxi)-6,7-dihidro-5H-imidazo[2,1-b][1,3]oxazín	Tratamiento de la tuberculosis
Swedish	(S)-2-nitro-6-(4-(trifluorometoxi)benziloxi)-6,7-dihidro-5H-imidazo[2,1-b][1,3]oxazínã	Behandling av tuberkulos
Norwegian	(S)-2-nitro-6-(4-(trifluorometoksy)benzyloksy)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oksazín	Behandling av tuberkulose
Icelandic	(S)-2-nítro-6-(4-(tríflúorómetoxý)benzýloxý)-6,7-dihýdró-5H-imídazó[2,1-b][1,3]oxazín	Meðferð við berklum