



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 December 2013
EMA/CHMP/771324/2013
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion¹ (initial authorisation)

Sirturo bedaquiline

On 19 December 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for the medicinal product Sirturo, 100mg tablets intended for the treatment of tuberculosis. Sirturo was designated as an orphan medicinal product on 26 August 2005. The applicant for this medicinal product is Janssen-Cilag International N.V. They may request a re-examination of any CHMP opinion, provided they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

The active substance of Sirturo is bedaquiline, a diarylquinoline for treatment of tuberculosis (ATC code J04AK05). Bedaquiline specifically inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an essential enzyme for the generation of energy in *Mycobacterium tuberculosis*. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli.

The benefits with Sirturo are its ability to likely provide clinically relevant activity as part of multi-drug regimens against tuberculosis (TB) based on clinical data in multidrug-resistant tuberculosis (MDR-TB) patients, who were defined as being at least resistant against the two major tuberculostatic medicines (isoniazide and rifampicine). In these studies, patients received Sirturo up to 24 weeks in combination with a background regimen (BR) of other anti-tuberculosis medicines in the treatment of pulmonary MDR-TB, and it was shown to be efficacious in terms of sputum culture conversion.

Further complementary evidence of efficacy is provided by data from an ongoing single arm study which also included patients with extensively drug resistant tuberculosis (XDR-TB)

The above studies also seem to indicate that bedaquiline currently does not show cross-resistance to any available tuberculosis medicines.

Additional studies are required post authorisation to further define the optimal use of this agent, both with regards the number and types of agents that are needed in combination, and the optimal treatment duration.

¹ Summaries of positive opinion are published without prejudice to the Commission decision, which will normally be issued 67 days from adoption of the opinion.



The most common side effects are increases in liver enzymes, which were noted in patients treated with bedaquiline compared to placebo. Liver enzymes are generally monitored during TB therapy, as liver toxicity is common for a number of other TB agents.

Furthermore, QTc prolongation was noted during treatment with bedaquiline. QTc prolongation requires monitoring and judicial consideration of benefit-risk when combining bedaquiline with other antimycobacterial drugs that are also significant prolongators of the QTc-interval.

A pharmacovigilance plan for Sirturo will be implemented as part of the marketing authorisation.

The approved indication is:

"For use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Consideration should be given to official guidance on the appropriate use of antibacterial agents".

It is proposed that Sirturo be prescribed by physicians experienced in the management of multi drug resistant *Mycobacterium tuberculosis*.

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers there to be a favourable benefit-to-risk balance for Sirturo and therefore recommends the granting of the marketing authorisation. The marketing authorisation is conditional².

² A conditional marketing authorisation is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact that additional data are still required. The marketing authorisation holder is likely to provide comprehensive clinical data at a later stage.