Report SIRTURO®Bedaquiline

Product& Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Bedaquiline **Brand Name:** SIRTURO® **Originator/licensee:** Janssen-Cilag International NV **Classification:** NI **ATC code:** J04AK05 **Orphan Status:** **Eu:** Yes **Us:** Yes **Mechanism of action:** Bedaquiline is a diarylquinoline. 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. [1]	**Authorized Indication:** **EMA**: bedaquiline is indicated for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) inpaediatric pts (five years to less than 18 years of age and weighing at least 15 kg) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. [1] **FDA:** bedaquiline is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in pediatric pts (five years and older and weighing at least 15 kg) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Bedaquiline is to reserve for use when an effective treatment regimen cannot otherwise be provided. [2] **Route of administration:** OS **Licensing status** **EU CHMP P.O. date:** 28 /01/2021 **FDA M.A. date:** 12/28/2012 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** Yes --- **ABBREVIATIONS:** **AE**: adverse event **CHMP**: Committee for Medicinal Products for Human Use **Tab**: tablet **M.A.**: Marketing Authorization **MDR-TB**: multidrug resistance tuberculosis **P.O.**: Positive Opinion **Pts**: patients **Qd**: once daily **SAE**: serious adverse event **TB**: tubercolosis **Tiw**: three times per week **TMC207**: bedaquiline **XDT-TB**: extremely multi-resistant TB	**Summary of clinical EFFICACY:** **Study TMC207-C211 (NCT02354014):** The single-arm, phase two study is designed to evaluate the safety, tolerability, pharmacokinetics and anti-mycobacterial activity of bedaquiline in combination with a background regimen of MDR-TB medications for the treatment of children and adolescents 0 months to <18 years of age who have confirmed or probable pulmonary MDR-TB. The study is composed of four age-based cohorts: in cohort one (≥ 12 to < 18 years)TMC207 tab is given orally as 400 mg, qd, for the first two weeks, followed by TMC207, 200 mg tiwper week for 22 weeks. Cohort two (≥ five to <12 years) TMC207 tab is given orally as 200 mg, qd, for first two weeks, followed by TMC207, 100 mg, tiw for 22 weeks. Cohorts three and four enrolled pts ≤ five years old. In cohort one, administration of bedaquiline in pts with culture positive pulmonary MDR-TB at baseline, resulted in conversion to a negative culture in 6/8 (75%) pts. The data released from cohort one (≥12 to <18 years and >30 kg) of study consisted of 15 pts. For the five-12 years age subgroup (cohort two), culture conversion was observed in 100% (3/3) of mycobacteria growth indicator tube evaluable pts (week 4, n=2; week 8, n=1). [3] **Summary of clinical SAFETY:** In phase two (cohort one: ≥12 to <18 years and >30 kg; 15 pts) trial, bedaquiline was found to be safe and well tolerated in pts with pulmonary MDR-TB. No deaths were observed. The most common AEs were arthralgia (40%), nausea (13%) and abdominal pain (13%). According to data from cohort two (pts aged 5-12 years), a SAE due to hepatotoxicity, three AEleading to treatment discontinuation, and eight grade 3/4 AE, were reported. There were no deaths. [3] **Ongoing studies:** • ***For the same indication:****Yes* • ***For other indications:*** *Yes* [Phase III, but if it is an O/OE drug, also Phase II] **Discontinued studies (for the same indication):***Yes* **References:** 1.https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-sirturo_en.pdf 2.https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204384s013lbl.pdf 3.https://adisinsight.springer.com/trials/700253748 4. https://www.drugs.com/price-guide/sirturo 5. https://www.epicentro.iss.it/tubercolosi/epidemiologia 6.https://apps.who.int/iris/bitstream/handle/10665/329395/9789289054447-eng.pdf 7.https://clinicaltrials.gov/ct2/show/NCT03384641?recrs=abdf&type=Intr&intr=sirturo&phase=12&draw=2&rank=2 8.https://clinicaltrials.gov/ct2/show/NCT02607449?recrs=abdf&type=Intr&cond=MDR-TB&phase=12&draw=3&rank=1	**Cost of therapy:** In EU, the cost of bedaquiline 100mg tabs to treat paediatric pts. weighing at least 15 kg for 24 weeks (corresponding to 96 tbs) is € 16 907[4]. **Epidemiology:** Italy is one of the countries with a low incidence of TB (<20/100,000 inhabitants). In 2017, 3.944 cases of tuberculosis were notified, which corresponds to an incidence in the population of 6.5/100,000 inhabitants. 66 cases ofMDR-TB, (2.5% of the total number of cases notified) were notified, being five extremely multi-resistant (XDT-TB). [5] **POSSIBLE PLACE IN THERAPY** (Guidelines, recommendations…) WHO guidelines for the management of MDR-TB in children and adolescents advocate for a fully oral regimen to be used, including three Group A* agents (levofloxacin -or moxifloxacin,bedaquiline and linezolid) and at least one Group B agent (clofazimina, or cycloserine or terizidone), such that at least four likely effective drugs are included at the beginning of treatment. If only one or two Group A agents are used, both Group B agents should be included in the regimen. When it is not possible to design an effective regimen (four likely effective agents) with Group A and Group B drugs, Group C agents (e.g., ethambutol, delamanid, pyrazinamid) should be used. [5] *Group A = considered highly effective and strongly recommended unless contraindicated; Group B= conditionally recommended as agents of second choice. [6] **OTHER INDICATIONS IN DEVELOPMENT:** Multibacillary leprosy, extensively drug resistant tuberculosis [7] **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** No **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** FS-1 [8] [if it is] *Service reorganization Y/N No *Possible off label use Y/N Yes