Summary of the risk management plan (RMP) for Sirturo (bedaquiline)

This is a summary of the risk management plan (RMP) for Sirturo, which details the measures to be taken in order to ensure that Sirturo is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Sirturo, which can be found on Sirturo's EPAR page.

Overview of disease epidemiology

Tuberculosis (TB) is an infectious disease that is caused by a bacterium called *Mycobacterium tuberculosis*. TB usually infects the lungs but can also affect other parts of the body such as the brain, kidneys and spine. There are two forms of the disease: latent TB and active TB. Latent TB is when the human immune system, the body's natural defences against germs and other substances that cause infection, fight the bacteria causing TB and prevent it from causing disease. The bacteria remain hidden or inactive without causing symptoms. Active TB is when the bacteria causing TB become active and make you sick. This can happen when the immune system is weakened, e.g., due to infection with the human immunodeficiency virus (HIV).

Patients with drug-susceptible TB (DS-TB) respond well to the medicines most commonly used to treat TB, which are called first-line anti-TB medicines. In patients with multidrug-resistant tuberculosis (MDR-TB), the TB bacteria have become resistant to first-line anti-TB medicines, and patients must be treated with combinations of other medicines, called second-line medicines, which may be less effective and more toxic.

Although MDR-TB has been reported all over the world, nearly 60% of all MDR-TB patients live in China, India, Russia and South Africa. Patients with MDR-TB have also been reported in Europe and the US but in smaller numbers. In 2011, 3.1% of the approximately 76,000 cases of TB in the European Union (EU) were MDR-TB. In the US, 1.3% of new TB patients were MDR-TB, and only 124 cases of MDR-TB were reported in 2011.

Of the 8.7 million people who develop TB each year, 1.1 million (13%) are also HIV-positive. In 2011, about 430,000 deaths from TB occurred in patients with HIV.

Summary of treatment benefits

Bedaquiline is a new anti-TB medicine used to treat adults with MDR-TB of the lungs and is always used in combination with other anti-TB medicines.

Bedaquiline has been studied in 2 major clinical trials, both of which measured the time from the start of bedaquiline treatment to the first negative (MDR-TB free) sputum (phlegm) culture.

The first of these trials included 161 patients with newly diagnosed MDR-TB who had never received anti-TB medicines and compared bedaquiline at a starting dose of 400 mg once a day for 2 weeks,

followed by 200 mg three times a week for 22 weeks, with placebo (no active medicine included in the tablet). All patients were also treated with a standard anti-TB medicine regimen that included 5 second-line medicines.

Conversion to a negative sputum culture was seen more frequently and was considerably faster in patients who were treated with bedaquiline than in patients who received placebo.

The second trial included 233 patients who were newly diagnosed with MDR-TB or had previously received anti-TB medicines. All patients received bedaquiline at a starting dose of 400 mg once a day for 2 weeks, followed by 200 mg three times a week for 22 weeks. In general, results for conversion to negative sputum culture were similar to the first trial.

Both clinical trials showed that bedaquiline is an effective treatment for MDR-TB.

Unknowns relating to treatment benefits

Patients who took part in the 2 clinical trials described above are representative of MDR-TB patients with regard to race and sex.

There is limited information about the use of bedaquiline in certain patient groups, including DS-TB patients, MDR-TB patients who are HIV-positive, and elderly patients.

No information is available about the use of bedaquiline in children and pregnant and breastfeeding women.

There is limited information on whether bedaquiline affects the risk of death in the years after being treated.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Increase in the QT interval (Electrocardiogram QT prolonged) The QT interval is a measurement on an electrocardiogram [ECG] which represents the time during which contraction of the heart ventricles occurs.	Some patients who received bedaquiline for 24 weeks experienced slight increases in the QT interval, but these increases went away after the patients stopped taking bedaquiline. There is a very small chance that an increase in QT interval may lead to more serious heart problems, such as abnormal heart rhythms (arrhythmias) which, very rarely, could lead to sudden death, although these types of problems were not seen during clinical trials. Patients who receive bedaquiline in combination with other medicines that increase the QT interval, including some anti-TB medicines, may be at higher risk for heart	Prolongation of the QT interval may be prevented by: - avoiding the use of bedaquiline in combination with other medicines that increase the QT interval, including some anti-TB medicines - performing frequent ECGs on patients receiving bedaquiline - avoiding the use of bedaquiline in patients with a history of increased QT interval or abnormal heart rhythm, including Torsade de Pointes (a type of abnormal beat of the heart's ventricles that is potentially life threatening); patients with a family history of increased QT interval; and patients with a history of decreased thyroid gland function.

Risk	What is known	Preventability
	problems.	

Important potential risks

Risk	What is known
Serious liver side effects (Severe hepatotoxicity)	During clinical trials, side effects involving the liver were seen more often in patients who received bedaquiline than in patients who did not. Most of these side effects were related to changes in the amount of liver enzymes, which speed up essential chemical reactions in the liver. Other medicines used to treat MDR-TB, including pyrazinamide, ethambutol, prothionamide, p-aminosalicyclic acid and linezolid, can cause side effects that involve the liver. During clinical trials, these medicines were often given together with bedaquiline, so it is not known in each case whether the liver side effects were due to bedaquiline, another anti-TB medicine, or a combination of anti-TB medicines .
Inflammation of the pancreas (Pancreatitis) The pancreas is an organ of the digestive system that produces enzymes that break down food and hormones that affect the level of sugar in the blood.	None of the patients who received bedaquiline during clinical trials developed inflammation of the pancreas while taking bedaquiline. A small number of patients reported other side effects related to the pancreas, e.g., increased blood levels of a pancreatic enzyme called amylase. There were no significant differences in levels of pancreatic enzymes between patients who received bedaquiline and patients who did not. Patients with TB who are HIV positive are more likely to develop side effects related to the pancreas.
Muscular disease resulting in muscular weakness (Myopathy)	Although there is no information about muscular disease in patients with MDR-TB, studies in animals suggest that bedaquiline may have an effect on the muscles attached to the skeleton (skeletal muscle). During clinical trials, patients who received bedaquiline had higher blood levels of lactate dehydrogenase, an enzyme that signals skeletal muscle damage, compared with patients who did not receive bedaquiline. None of the patients who received bedaquiline during clinical trials developed muscular disease. Among patients who received bedaquiline and patients who did not, a small number developed muscle pain.
Damage to the heart muscle (Myocardial injury)	Two patients who received bedaquiline in combination with other anti-TB medicines died due to heart problems (both after the last intake of bedaquiline). However, these deaths were not thought to be related to bedaquiline. There were no significant differences in levels of heart enzymes in patients who received bedaquiline compared with those who did not. Other medicines that were part of the MDR-TB treatment regimen, such as ethambutol, are known to cause inflammation of the heart muscle and may be associated with heart problems.
Development of drug resistance	In some patients the bacteria that cause TB become resistant to anti-TB

Risk	What is known
	medicines. This is more likely to occur when patients stop taking several anti-TB medicines or when patients are treated with only one anti-TB medicine instead of a combination of anti-TB medicines. When the bacteria become resistant to first-line anti-TB medicines, other anti-TB medicines may not be as effective, which decreases the number of treatment options available to the patient. Bedaquiline attacks the bacteria that cause TB in a way that is different from other anti-TB medicines. Resistance to bedaquiline may also occur if patients are treated with a combination of anti-TB medicines that includes a dose of bedaquiline that is lower than the recommended dose. During clinical trials, patients with bacteria that were less responsive to bedaquiline were often also less responsive to the second-line anti-TB medicine clofazimine.
Off-label use, including prolonged duration of treatment Off-label use is use of a medicine in patients for whom the medicine is not approved or in an unapproved way	Bedaquiline may be inappropriately used in patients for whom the drug is not intended, including: - patients with TB sensitive to first-line medicines (DS-TB); - patients with latent-TB infection; - children and adolescents under 18 years of age; - patients with TB that affects other parts of the body such as the brain, kidneys, and spine; - patients infected with types of mycobacteria other than those that cause TB; - patients using the medicine for longer than 24 weeks (in patients with extensive drug resistance, when treatment with bedaquiline beyond 24 weeks is necessary to get cured, a longer duration of treatment may be considered, but only on a case-by-case basis and under close safety monitoring) - patients using the medicine as the only treatment in an MDR-TB regimen without combining it with the other anti-TB medicines. Use of bedaquiline in patients for whom the medicine is not intended does not necessarily increase the risk of side effects.
Medication error	Bedaquiline is available as a 100-mg tablet. The recommended dose of bedaquiline for patients with MDR-TB is 400 mg once a day for the first 2 weeks, followed by 200 mg three times a week, at least 2 days apart, for the next 22 weeks. The switch from the 400 mg dose to the 200 mg dose may lead to mistakes in how much bedaquiline a patient takes. Because bedaquiline must always be taken in combination with 3 other anti-TB medicine, each with a specific dosing regimen, mistakes can occur,

Risk	What is known
	resulting in administration of too little or too much medicine. It is recommended that bedaquiline intake is supervised as is done for other anti-TB medicine .

Missing information

Risk	What is known
Long-term effects of bedaquiline treatment on death (mortality)	There is limited information on the long-term effects of bedaquiline on the rate of death among patients taking bedaquiline.
Use in patients with serious liver problems (Use in patients with severe hepatic impairment)	No change in the dose of bedaquiline is required in patients with mild or moderate decrease in liver function. Bedaquiline should be used with caution in patients with moderate decrease in liver function. Because no patients who took part in bedaquiline clinical trials had serious liver problems, no information about the safety and effectiveness of bedaquiline in such patients is available. Use of bedaquiline in patients with serious liver problems is not recommended.
Use in patients with serious kidney problems (Use in patients with severe renal impairment)	No change in the dose of bedaquiline is required in patients with mild or moderate decrease in kidney function. Because no patients who took part in bedaquiline clinical trials had serious kidney problems, no information about the safety and effectiveness of bedaquiline in such patients is available. Bedaquiline should be used with caution in patients with serious kidney problems.
Use in children and adolescents less than 18 years of age (Use in paediatric patients)	Because bedaquiline has not been studied in children and adolescents under 18 years of age, no information about its safety and effectiveness in these patients is available. For this reason, the use of bedaquiline in children and adolescents under the age of 18 is not recommended.
Use in patients 65 years of age or older (Use in elderly patients)	Because only 2 patients in bedaquiline clinical trials were 65 years of age or older, information about the safety and effectiveness of bedaquiline in such patients is limited. In general, elderly patients are more likely to have other diseases, including liver and kidney problems, and are more likely to take multiple medicines. As a consequence, bedaquiline treatment should be used with caution in elderly patients.
Use during pregnancy	Because bedaquiline has not been studied in pregnant women, no information about its safety and effectiveness during pregnancy is available. For this reason, the use of bedaquiline in pregnant women is not recommended unless consultation with a healthcare professional determines that the benefits of treatment are considered to outweigh the potential risks.
Use in breastfeeding women	It is not known whether bedaquiline passes into human breast milk. A decision should be made in consultation with a healthcare professional as to whether to discontinue breastfeeding or to discontinue or abstain from

Risk	What is known
	bedaquiline therapy, taking into account the benefit of breastfeeding for the infant and the benefit of bedaquiline therapy for the mother.
Use in patients with risk factors for heart diseases (Use in patients with cardiovascular risk factors)	Because bedaquiline clinical trials did not include patients with heart disease or serious risk factors for heart problems, its safety and effectiveness in these patients is not known. For this reason, the use of bedaquiline in patients with heart disease or serious risk factors for heart problems is not recommended unless a healthcare professional determines that the benefits of treatment outweigh the potential risks. Patients who participated in bedaquiline clinical trials were regularly monitored (vital signs, ECGs) for signs of heart problems. If a patient develops a prolonged QT interval or an abnormal heart rhythm, bedaquiline treatment must be stopped.
Use in patients with MDR-TB and HIV infection (Use in HIV coinfection)	Because bedaquiline has been studied in only a small number of patients with both TB and HIV infection, little information about its safety and effectiveness in such patients is available. Therefore, patients with both TB and HIV infection who were taking anti-HIV drugs were not allowed to participate in bedaquiline clinical trials. No information is available about patients who take anti-HIV medicines with bedaquiline or have a CD4+ count below 250 cells/microlitre when starting bedaquiline treatment. The bedaquiline prescribing information lists medicines that should not be used with bedaquiline or that should be used with caution, as well as medicines that require specific monitoring.
Effects on fundic glands The fundic glands are located in the stomach and release hormones.	Studies of bedaquiline in animals were conducted prior to studies in humans. In some mice and dogs that were given bedaquiline, the fundic glands started to degenerate, or waste away. In the animals that developed degeneration of the fundic glands, no effect on the levels of hormones in the stomach were seen. When bedaquiline treatment was stopped, the fundic glands began to recover. It is not clear whether this same effect occurs in humans.
Drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters Drug-metabolising enzymes are responsible for the biochemical modification of medicines in the body. Transporters are proteins involved in the movement of medicines across a biological	There is limited information on the interaction of bedaquiline with potent inhibitors of drug-metabolising enzymes and transporters.

Risk	What is known
membrane.	

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Sirturo can be found on Sirturo's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
1692-0049281/ FK 10493	To assess the potential of bedaquiline and its M2 metabolite to inhibit OATP1B1 and OATP1B3 and to be substrates for OATP1B1 and OATP1B3.	Missing information: - Drug-drug interactions with potent inhibitors of drug-metabolising enzymes (responsible for the biochemical modification of medicines in the body) and transporters (proteins involved in the movement of drugs across a biological membrane).	Planned	Submission final report: 1Q 2014
1692-0049280/ FK 10497	To assess the potential of bedaquiline and M2 to inhibit OCT1 and to be substrates for OCT1.	Missing information: - Drug-drug interactions with potent inhibitors of drug-metabolising enzymes (responsible for the biochemical modification of medicines in the body) and transporters (proteins involved in the movement of drugs across a biological membrane).	Planned	Submission final report: 1Q 2014
1692-0055447/FK 10603	To assess whether bedaquiline and M2 are substrates for BCRP, BSEP and MRP2.	Missing information: - Drug-drug interactions with potent inhibitors of drug-metabolising enzymes (responsible for the biochemical modification of medicines in the body) and transporters (proteins involved in the	Planned	Submission final report: 1Q 2014

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
		movement of drugs across a biological membrane).		
1692-0054807/ FK 10542, CYP2C8 and CYP2C9 inhibition by TMC207 (microsomes)	To assess the potential of bedaquiline to inhibit the enzymes CYP2C8 and CYP2C9.	Missing information: - Drug-drug interactions with potent inhibitors of drug-metabolising enzymes (responsible for the biochemical modification of medicines in the body) and transporters (proteins involved in the movement of drugs across a biological membrane).	Planned	Submission final report: 1Q 2014
1692-0055364/FK 10608	To assess the potential of bedaquiline and M2 to inhibit BCRP and OAT1.	Missing information: - Drug-drug interactions with potent inhibitors of drug-metabolising enzymes (responsible for the biochemical modification of medicines in the body) and transporters (proteins involved in the movement of drugs across a biological membrane).	Planned	Submission final report: 1Q 2014
1692-0055365	To assess the potential of bedaquiline and M2 to inhibit OAT3.	Missing information: - Drug-drug interactions with potent inhibitors of drug-metabolising enzymes (responsible for the biochemical modification of medicines in the body) and transporters (proteins involved in the movement of drugs across a biological membrane).	Planned	Submission final report: 1Q 2014
1692-0055366/FK 10604	To assess the potential of bedaquiline and M2 to inhibit OCT2, MATE1 and MATE2.	Missing information: - Drug-drug interactions with potent inhibitors of drug-metabolising enzymes (responsible for the biochemical modification of medicines in the body) and transporters (proteins involved in the movement of drugs across a biological membrane).	Planned	Submission final report: 1Q 2014
Preclinical experiments	To explore mechanisms of resistance other than the ones known to date.	Important potential risk: - Development of drug resistance (drug resistance is the ability of bacteria to replicate in the presence of the drug concentration which is expected to prevent	Planned	Submission final report: 1Q 2015

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
		such replication).		
STREAM	To evaluate additional efficacy and safety data of bedaquiline in different treatment regimens compared to a regimen that does not include bedaquiline (confirmatory Phase 3 study)	Important identified risk: - Increase in the QT interval (The QT interval is a measurement on an electrocardiogram [ECG] which represents the time during which contraction of the heart ventricles occurs). Important potential risk: - Serious liver effects. - Inflammation of the pancreas. - Muscular disease resulting in muscular weakness. - Damage to the heart muscle. - Development of drug resistance (Drug resistance is the ability of bacteria to replicate in the presence of the drug concentration which is expected to prevent such replication). - Off-label use, including prolonged duration of treatment (Off-label use is use of a medicine in patients for whom the medicine is not approved). - Long-term effects of bedaquiline treatment on death. - Use in patients 65 years of age or older. - Use in patients with MDR-TB and HIV infection. - Effects on fundic glands (The fundic glands are located in the stomach and release hormones). - Drug-drug interactions with potent inhibitors of drug-metabolising enzymes (responsible for the biochemical modification of medicines in the body) and transporters (proteins involved in the movement of drugs across a biological membrane).	Planned	Annual updates on study progress in the frame of annual renewal submissions Interim IDMC analysis when half of the patients reach W68: 1Q 2018 Report W68 primary analysis: 3Q 2020 Report W92 analysis: 1Q 2021 Report W132 final analysis: November 2021

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Multi-Country MDR-TB Disease Registry	To evaluate the effectiveness, safety and drug resistance of bedaquiline when added to a background regimen (selection of commonly used anti-TB medicines).	Important identified risk: - Increase in the QT interval (The QT interval is a measurement on an electrocardiogram [ECG] which represents the time during which contraction of the heart ventricles occurs). Important potential risk: - Serious liver effects. - Inflammation of the pancreas. - Muscular disease resulting in muscular weakness. - Damage to the heart muscle. - Development of drug resistance (Drug resistance is the ability of bacteria to replicate in the presence of the drug concentration which is expected to prevent such replication). - Off-label use, including prolonged duration of treatment (Off-label use is use of a medicine in patients for whom the medicine is not approved). - Medication error - Long-term effects of bedaquiline treatment on death. - Use in patients 65 years of age or older. - Use in patients with MDR-TB and HIV infection. - Effects on fundic glands (The fundic glands are located in the stomach and release hormones). - Drug-drug interactions with potent inhibitors of drug-metabolising enzymes (responsible for the biochemical modification of medicines in the body) and transporters (proteins involved in the movement of drugs across a biological membrane).	Planned	Semiannual (Interim reports) Q2 2020 (Final study report)

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
US Exposure Registry	The aim is to describe the indication and utilisation of bedaquiline, patient outcomes, drug susceptibility and the occurrence of adverse events.	- Development of drug resistance (drug resistance is the ability of bacteria to replicate in the presence of the drug concentration which is expected to prevent such replication). - Long-term effects of bedaquiline treatment on death.	Ongoing	2019
TMC207TBC1002	To assess how much bedaquiline enters the blood after taking a single dose of bedaquiline, using 2 different forms of the medicine (a tablet and a water dispersible tablet), with and without food.	Short-term safety of bedaquiline after one dose in adults Missing information: - Use in children and adolescents less than 18 years of age.	Ongoing	2014 (Final study report)
TMC207-C211	To assess the pharmacokinetics (how the drug is absorbed, distributed and eliminated by the body), effectiveness, safety and tolerability of bedaquiline in children and adolescents. (from ≥12 to <18 years; from ≥5 to <12 years; from ≥ 2 to <5 years; and <2 years of age)	Missing information: - Use in children and adolescents less than 18 years of age.	Planned	2022 (Final study report)
Expanded Access Program (EAP)	To provide early access to bedaquiline for patients with pre-XDR TB (resistant to a few defined anti-TB medicines) and XDR-TB (resistant to at least 4 important anti-TB medicines).	Provide safety information on pre-XDR and XDR-TB patients. Important identified risk: - Increase in the QT interval (The QT interval is a measurement on an electrocardiogram [ECG] which represents the time during which contraction of the heart ventricles occurs).	Ongoing	2017 (Final study report)

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
		Important potential risks: - Serious liver effects. - Inflammation of the pancreas. - Muscular disease resulting in muscular weakness. - Damage to the heart muscle.		
Drug resistance surveillance	The aim of the drug resistance surveillance is to monitor bedaquiline susceptibility profile over time.	Development of drug resistance (Drug resistance is the ability of bacteria to replicate in the presence of the drug concentration which is expected to prevent such replication).	Planned	2019

Studies which are a condition of the marketing authorisation

Studies 1692-0049280/FK 1049, 1692-0049281/FK 10493, 1692-0055447/FK 10603, 1692-0054807/FK 10542, 1692-0055364/FK 10608, 1692-0055365 and 1692-0055366/FK 10604 are conditions of the marketing authorisation.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable

This summary was last updated in 01-2014.