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# Summary of the risk management plan (RMP) for Sivextro (tedizolid)

This is a summary of the risk management plan (RMP) for Sivextro, which details the measures to be taken in order to ensure that Sivextro 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 Sivextro, which can be found on Sivextro's EPAR page.

## Overview of disease epidemiology

Sivextro is an antibiotic used to treat acute (short-term) bacterial infections of the skin and of skin structures (tissue below the skin) such as cellulitis (inflammation of the deep skin tissue), skin abscesses and wound infections. Skin infections are among the most common infections seen in the community and the hospital.

Skin infections are typically caused by bacteria that live on the skin as part of the natural flora, such as *Staphylococcus aureus* and *Streptococcus pyogenes*. Some of these bacteria may become resistant and can no longer be killed by the more commonly used antibiotics as is the case for a bacterium called methicillin-resistant *Staphylococcus aureus* (MRSA). The percentage of MRSA infections ranges from 10 to 40% in European hospitals.

## Summary of treatment benefits

Sivextro contains the active substance tedizolid, which is a type of antibiotic called an oxazolidinone. Sivextro was compared with linezolid (another oxazolidinone) in two main studies involving a total of 1,333 patients with acute bacterial infections of the skin and of skin structuress. These also included infections caused by MRSA. In both studies patients received 6 days of treatment with Sivextro which was compared with a 10-day treatment of linezolid. The main measure of effectiveness in both studies was the number of patients whose infection was cured after treatment.

Sivextro was at least as effective as linezolid at curing the infection. 85.5% of patients treated with Sivextro in the first study and 88.0% in the second study were cured, compared with 86.0% and 87.7% respectively of patients treated with linezolid.

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## Unknowns relating to treatment benefits

In the main studies, most (85%) patients were white adults under 65 years of age, only a minority (8%) of patients were diabetic, and less than 2% of patients were HIV positive. There are no efficacy data in patients with a weakened immune system (e.g., low white blood cells/severe immunosuppression). Safety and efficacy of Sivextro when administered for longer than 6 days have not been established.

## Summary of safety concerns

***Important identified risks***

| Risk | What is known | Preventability |
|---|---|---|
| Myelosuppression: decreases blood platelets (cells that help form clots to prevent bleeding), decreased haemoglobin (part of red blood cells responsible for transporting oxygen), and decreased neutrophils (a type of white blood cell) | A medicine similar in structure to Sivextro called linezolid is known to cause these side effects when used for a long period (typically more than 2 weeks). In clinical trials with Sivextro, anaemia (decreased levels of haemoglobin in the blood) was reported in 6 out of 1,000 patients, and decreased white blood cell counts in 1 out of 1,000 patients. | Sivextro should not be taken for longer than the recommended duration of 6 days after which the risk of side effects on the blood may increase. |
| Antibiotic-associated diarrhoea (*C. difficile*-associated diarrhoea, CDAD) | Antibiotic-associated diarrhoea refers to diarrhoea that develops in a person who is taking or recently took antibiotics. Some antibiotics can decrease protective normal bacteria in the gut, and when this happens, harmful bacteria may be able to multiply and cause symptoms such as cramping pain, fever, and diarrhoea, sometimes occurring more than 2 months after receiving antibiotic treatment. One of the most serious causes of antibiotic-associated diarrhea is infection with a bacterium, *Clostridium difficile*, which can occasionally be severe in some patients if not treated promptly. Only 1 case of antibiotic-associated CDAD has been reported to date in | Ensuring that antibiotics are only used when necessary will limit cases of antibiotic-associated diarrhoea. The spread of the bacteria causing CDAD can be reduced with careful handwashing and isolation of infected patients.<br><br>Patients should tell their doctor or pharmacist if they are suffering from diarrhoea before they take Sivextro or if they have suffered from diarrhoea whilst taking antibiotics in the past.<br><br>Patients should contact their doctor straight away if they suffer from diarrhoea during or after Sivextro treatment. However, no treatment should be taken by the patient to treat their diarrhoea without first checking with their doctor. If CDAD is confirmed, the doctor should discontinue Sivextro, start supportive measures and antibiotic |

| Risk | What is known | Preventability |
|---|---|---|
| | clinical trials with Sivextro. | treatment for *C. difficile* may be given. |

***Important potential risks***

| Risk | What is known |
|---|---|
| Serotonin syndrome (serious symptoms affecting the nervous system caused by increased levels of serotonin in the brain) | Linezolid, an antibiotic similar to Sivextro has been associated with serotonin syndrome when taken together with some other medicines (e.g., some antidepressants). Serotonin syndrome is a serious condition and symptoms can include high fevers, shivering, sweating, tremors (shakiness), confusion, agitation, rigidity, and loss of coordination. Tests carried out so far do not suggest a similar risk with Sivextro; however, potential interactions between Sivextro and other medicines that increase serotonin levels in the blood have not been studied in clinical trials. |
| Development of antibiotic resistance (when bacteria are able to survive after treatment with one or more antibiotics) | There are no data from clinical trials on the risk of resistance of bacteria to Sivextro in patients. Prescribing Sivextro in the absence of a proven or strongly suspected bacterial infection increases the risk of the development of drug-resistant bacteria. Doctors are therefore advised to consider official guidance on the appropriate use of antibiotics when considering prescribing Sivextro. |
| Risk for nerve damage and vision problems from long term use | Prolonged use of linezolid, an antibiotic similar to Sivextro, has been associated with changes in vision and changes in sensation in hands or feet (tingling pain or loss of sensation). No nerve or vision problems were observed in experimental models with Sivextro. These effects are unlikely to occur with the recommended dose duration of 6 days. |
| Risk for lactic acidosis (a build-up of lactic acid in the blood) from long term use | Prolonged use of linezolid, an antibiotic similar to Sivextro, has been associated with build-up of lactic acid in the blood, often causing nausea (feeling sick) or vomiting. These effects are unlikely to occur with the recommended dose duration of 6 days. |

***Missing information***

| Risk | What is known |
|---|---|
| Prolonged treatment for more than 7 days | The longest duration Sivextro has been given for in clinical trials was 7 days. There are no data to assess the potential risks of prolonged treatment with Sivextro for more than 7 days for complicated or chronic (long-term) skin/soft tissue structure infections (e.g. diabetic foot infections, bedsores, vascular ulcers, gangrene, etc.). The recommended duration of use is 6 days and Sivextro should not be used for longer. |
| Treatment of infections of the skin or under the skin in | Patients with low blood cell counts or weakened immune systems were not studied in clinical trials, thus the effectiveness of Sivextro in such patients is not known. In an experimental model of infection, the antibacterial activity of |

| Risk | What is known |
|---|---|
| patients with severely weakened immune system (e.g., low white blood cells, or transplant patients) | Sivextro was reduced in the absence of white blood cells. Alternative antibiotics should be considered when treating patients with very low levels of white blood cells. |
| Pregnant or breastfeeding women | There are no data from the use of Sivextro in pregnant women. As a precaution, Sivextro should not be used during pregnancy.<br><br>It is unknown whether tedizolid passes into breast milk of women administered Sivextro. A decision must be made as to whether to stop breastfeeding or to stop Sivextro, taking into account the benefits and risks of treatment and of breastfeeding for the mother and child. |
| Treatment of elderly patients, diabetic patients and patients with polymicrobial infections (infections caused by more than one type of bacteria, such as traumatic wounds, bite wounds, major abscesses, etc.) | No dosage adjustment of Sivextro is necessary in elderly patients. Based on safety data in 81 elderly patients, safety was similar to the safety in adults (18-64 years old). A total of 30 diabetic patients with acute bacterial skin infections were enrolled in uncontrolled studies with Sivextro in doses of 200 mg or more by mouth for 5-7 days, and 58 patients with diabetes were studied in Phase 3 controlled studies with Sivextro 200 mg by mouth or injection into a vein for 6 days. The amount of tedizolid in the blood was similar between diabetic versus non-diabetic patients in a clinical study. There were few patients enrolled with these kinds of polymicrobial infections in clinical studies. |
| Potential for Sivextro to affect medicines that are broken down by an enzyme called CYP 3A4 or medicines that are removed from cells by breast cancer resistance protein (BCRP) or organic anion transporting polypeptide (OATP-1B1) | In vitro studies showed that Sivextro could induce the enzyme CYP 3A4 which could potentially accelerate the way other medicines are broken down in the body and thereby reducing their effectiveness. There are no clinical data to assess the potential risk for interactions between Sivextro and other medicines which are broken down by the enzyme CYP 3A4.<br><br>Experimental studies showed that Sivextro blocks BCRP and OATP-1B1 which could lead to increased blood levels of medicines (e.g. imatinib, lapatinib, statins such as pitavastatin, rosuvastatin, atorvastatin, fluvastatin, and lovastatin; sulfasalazine, topotecan, repaglinide, bosentan, valsartan, olmesartan, and glyburide) that are removed from cells by these routes. However, there are no clinical data to assess the potential risk for these type of interactions. If possible, temporarily stopping the other medicine should be considered during the 6 days of treatment with Sivextro. |
| Potential for Sivextro to cause heart beat irregularities in people with pre-existing heart disease | There were some changes in the electrocardiograms (ECGs) in a few patients with heart failure or other conditions that may increase the chances of having a more serious heart rhythm problem. No patients developed heart problems due to Sivextro in clinical trials, but the potential risk needs to be evaluated further in clinical experience. |

## 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 Sivextro can be found on Sivextro'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** |
|---|---|---|---|---|
| Long Term Safety Study Of Tedizolid Phosphate In The Treatment Of Serious Gram Positive Infections | To study the safety of tedizolid when it is administered as long-term treatment for Gram-positive infections. | Long-term safety and potential for adverse effects on the blood, nerve damage, vision problems, or problems caused by a build-up of lactic acid in the blood. | Planned | Final report planned 2Q 2018 |
| Five-year in vitro surveillance study | Evaluate the potential for emergence of drug resistance in clinical Gram-positive isolates. | Monitor cross-resistance between linezolid and tedizolid mediated by L3 or L4 ribosomal protein mutations or *cfr* gene | Planned to start Jan.2015 | Annually 2016-2020 |
| Drug-drug interaction study | Evaluate the potential for drug-drug interaction mediated by induction of CYP3A4. | Interaction study in healthy volunteers administered midazolam with oral tedizolid at steady state. | Planned to start 3Q 2015 | Final report planned 1Q 2016 |
| Phase 3 Efficacy in treatment of ABSSSI in Asian patients (Bayer ABSSSI Phase 3 trials in China and Japan) | Effectiveness and safety of tedizolid compared with standard treatment. | Efficacy in Asian adults (over 18 years). | China: Initiation 1 Q2014<br>Japan: Initiation 4 Q2013 | Approximately 2016 |

***Studies which are a condition of the marketing authorisation***

None of the above studies are conditions of the marketing authorisation.

## Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in 03-2015.