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Summary of the risk management plan (RMP) for Orbactiv (oritavancin)

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

Overview of disease epidemiology

Orbactiv is an antibiotic used in adults to treat acute (short-term) bacterial infections of the skin and skin structures (tissue below the skin) such as cellulitis (inflammation of the deep skin tissue), skin abscesses and wound infections.

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

Orbactiv contains the active substance oritavancin, which is a type of antibiotic called a glycopeptide. A single dose of Orbactiv was compared with a 10-day treatment with vancomycin (another glycopeptide) in two main studies involving a total of around 1959 patients with acute bacterial infections of the skin and of skin structures, such as cellulitis, skin abscesses and wound infections. These also included infections caused by MRSA.

In both studies, the main measure of effectiveness was the number of patients who responded within 3 days of starting treatment with an improvement in their skin in the infected area, lack of fever and no need for additional antibiotic.

Orbactiv was at least as effective as vancomycin at curing the infection. In the two studies, 80.1% and 82.3% respectively of patients treated with Orbactiv responded to treatment, compared with 82.9% and 78.9% respectively of patients treated with vancomycin.

Unknowns relating to treatment benefits

Oritavancin has not been studied in patients who are pregnant or breastfeeding and in patients below 18 years of age.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions (hypersensitivity)	Serious allergic reactions (rash, itching, redness, problems with breathing) have been seen following treatment with Orbactiv. In a clinical study 7 out of 100 people treated with Orbactiv had an allergic reaction compared with 14 out of 100 patients who took vancomycin. patients who had an allergic reaction following a glycopeptide other than Orbactiv are likely to also be allergic to Orbactiv (this is referred to as cross-sensitivity).	Patients who have had an allergic reaction to Orbactiv or one of its ingredients should not be given Orbactiv. If an allergic reaction occurs while receiving Orbactiv, treatment with this medicine should be stopped immediately and supportive care should be given. Patients who had an allergic reaction to similar antibiotics should be monitored carefully during and after the infusion.
Interaction with warfarin (a blood-thinning medicine used to prevent blood clots)	Orbactiv may increase the levels of warfarin in the blood of patients given both medicines, which may increase the risk of bleeding (nose bleeds, gum bleeds, bleeding more than usual from a cut).	Patients on long-term treatment with warfarin should only receive Orbactiv when the benefits of treatment outweigh the risks. Patients who receive warfarin and Orbactiv should be closely monitored for signs of bleeding.
Blood clotting test interference (coagulation test interference)	Although Orbactiv has no effect on blood clotting it has been shown to interfere with substances commonly found in some laboratory blood clotting tests, leading to falsely raised results. Test results are expected to remain falsely elevated for 24 to 48 hours after Orbactiv administration.	Patients who require blood coagulation monitoring should have alternative tests that are not affected by Orbactiv. Patients should not receive a blood thinner called 'unfractionated heparin' within 48 hours of receiving Orbactiv.
Accumulation of pus (abscess) underneath the skin and in the limbs	New abscesses have been seen with Orbactiv treatment. Patients may experience mild to severe symptoms, including fever, pain, redness of the skin, swelling and warmth around the area of the abscess, and swollen lymph nodes.	Doctors should monitor patients for new infection at another site on the skin and take appropriate measures if abscesses occur.

Important potential risks

Risk	What is known
Antibiotic-associated diarrhoea/infectious diarrhoea (pseudomembranous colitis/ *C. difficile*	Antibiotic-associated diarrhoea refers to diarrhoea that develops in a person who is taking or recently took antibiotics. Some antibiotics can decrease the levels of protective bacteria normally found 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

Risk	What is known
associated diarrhoea CDAD)	after receiving antibiotic treatment. One of the most serious causes of antibiotic-associated diarrhoea is infection with a bacterium called *Clostridium difficile.* Antibiotic-associated diarrhoea has been reported with Orbactiv. Patients who experience prolonged or severe diarrhoea following their treatment with Orbactiv should contact their healthcare provider. Appropriate treatment should be considered.
Infection or inflammation of the bones or bone marrow (osteomyelitis)	More cases of osteomyelitis were reported with Orbactiv than with vancomycin. Patients should be monitored for signs and symptoms of osteomyelitis following treatment with Orbactiv. If osteomyelitis is diagnosed or suspected, alternative antibiotic treatment should be started. Oritavancin is not approved for the treatment of bone or bone marrow infections. Patients suspected or confirmed to have underlying bone or bone marrow infections should receive appropriate treatment.
Development of resistant bacteria	Patterns of antibiotic usage may affect the number of resistant organisms to any class of antibiotics. The factors contributing to development of resistance to Orbactiv are unknown. However, factors that may contribute toward resistance development include incorrect diagnosis of the infection and unnecessary or inappropriate antibiotic use. Orbactiv should only be used to treat bacterial infections. Treating with Orbactiv in the absence of a proven or strongly suspected bacterial infection is unlikely to be helpful to the patient and is a potential risk for the development of drug-resistant bacteria.
Increased uric acid in the blood (hyperuricaemia)	Increased uric acid in the blood, seen with other antibiotics such as vancomycin, has also been seen with the use of Orbactiv in some studies. Patients with a history of increased uric acid or gout should discuss this with their healthcare provider prior to taking Orbactiv.
Use of Orbactiv other than the approved use (off-label use)	There is a potential risk that Orbactiv may be used for infections against which it has not been proven to be effective. Such use is unlikely to provide any benefits to the patient and is likely to delay appropriate treatment.
Kidney damage (renal impairment)	Kidney damage is a known complication of vancomycin, another glycopeptide. Although mainly seen in animal studies, kidney damage has also occurred in a small number of patients who were using Orbactiv. Dosage adjustment of Orbactiv is not needed in patients with mild or moderate renal impairment.
Anticholinergic effects (effects such as constipation, dizziness and abnormal heart rate)	Animal studies have shown that Orbactiv blocks the effects of the neurotransmitter acetylcholine, an important substance in the nervous system. This can lead to anticholinergic effects such as constipation, dizziness, and abnormally rapid heart rate. These effects occurred in clinical studies at a rate similar for Orbactiv and vancomycin.
Antidopaminergic effects (effects affecting physical movement such as muscle spasms)	Animal studies have shown that Orbactiv blocks the effects of the neurotransmitter dopamine, a substance in the nervous system important for physical movement. Antidopaminergic effects such as muscle spasms occurred in clinical studies at a rate similar for Orbactiv and vancomycin.
Abnormalities with the transmission of	Abnormal heart rhythm has been seen with the use of Orbactiv. Patients with pacemakers or a history of heart conditions should speak to their healthcare

Risk	What is known
electrical impulses through the heart which could lead to abnormal heart rhythm (cardiac conduction abnormalities)	provider prior to treatment with Orbactiv.
Hearing abnormalities (ototoxicity)	Ototoxicty is a known complication of glycopeptides such as vancomycin. Hearing loss, and ringing in the ears has also been seen with the use of Orbactiv.

Missing information

Risk	What is known
Limited information on use during pregnancy and breastfeeding	Animal studies of Orbactiv revealed no evidence of harm to the fetus. In the absence of studies in pregnant women, Orbactiv should only be used during pregnancy if the potential benefit outweighs the potential risk to the fetus. Studies of Orbactiv in animals have also shown excretion of Orbactiv in milk. In the absence of studies in nursing mothers, Orbactiv should only be used during breastfeeding if the potential benefit outweighs the potential risk.
Use of Orbactiv in patients under 18 years of age	The safety and effectiveness of Orbactiv in patients less than 18 years of age has not been established.

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 Orbactiv can be found on Orbactiv'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**
14-TMC-01: International Oritavancin Surveillance Protocol	To monitor the activity of oritavancin compared to numerous broad- and narrow-spectrum (Gram-positive-targeted) antibacterial agents when tested against contemporary clinical samples collected in US and European medical centers for the years 2014 to 2019.	Development of drug-resistant bacteria	Protocol finalised on 2 July 2014	Annually for the first 5 years following approval
TMC-ORI-11-01 An Open Label, dose finding, pharmacokinetics, safety, and tolerability study of Oritavancin single dose infusion in pediatric subjects less than 18 years of age with suspected or confirmed bacterial infections	Primary objective: Measure of distribution of the Oritavancin in the body (Pharmacokinetics [PK]) using variables such as Cmax and AUC Secondary objectives: PK variables of half-life, Tmax, Vd, and CL Safety of oritavancin assessed according to clinical laboratory parameters, adverse events, serious adverse events up to 60 days following termination of study drug infusion.	Safety, tolerability and dose finding of oritavancin in patients less than 18 years of age.	Started	30 September 2017
TMC-ORI-11-02 A multicenter, evaluator-blind, randomised study to evaluate the safety and tolerability of single dose IV oritavancin versus vancomycin for	Primary objective: Safety of oritavancin relative to comparator assessed according to vital signs, laboratory abnormalities, all-cause mortality, and the incidence and time to resolution of adverse events and serious advert events.	Safety and tolerability and effectiveness of oritavancin in patients less than 18 years of age.	Planned	15 December 2020

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
the treatment of pediatric patients with acute bacterial skin and skin structure infection	Secondary objectives: Clinical response (clinical cure) of treatment with single-dose IV oritavancin compared with vancomycin at Day 14 and the post therapy evaluation visit in the modified Intent-to-Treat (mITT) population. Early clinical response (≥20% lesion size reduction from baseline) of treatment with single dose IV oritavancin compared with vancomycin at the early clinical evaluation visit in the mITT population.			
Open-label trial evaluating the safety of a single 1200 mg IV dose of Orbactiv in patients on concomitant chronic warfarin therapy who are being treated for ABSSSI	The key objectives of this study are to characterise the effect of oritavancin on clinical care and warfarin dosing in patients on chronic warfarin therapy, to determine the magnitude and duration, if any, of alterations to warfarin dosing, and to determine the safety of, and clinically important consequences which may result from the concomitant use of warfarin and oritavancin.	The safety of and clinically important consequences which may result from the concomitant use of warfarin and oritavancin.	Planned	August 2016
Open-label trial to assess the clinical significance of the DDI between a single 1200 mg IV dose of Orbactiv and warfarin in healthy volunteers	The key objectives of this dedicated warfarin drug interaction study are to evaluate the effects of a single 1200 mg infusion of oritavancin on the safety and PK of warfarin and to determine the magnitude and duration of this interaction to gain insights into the possible need for	The magnitude and duration of the DDI between a single 1200 mg IV dose of Orbactiv and warfarin.	Planned	June 2015

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	alterations in warfarin dosing.			
Effects of oritavancin on phospholipid and nonphospholipid based coagulation test in vitro	The objective of this study will be to determine which tests used to monitor anticoagulant therapy may be used in patients following a single 1200 mg dose of oritavancin.	Interference with coagulation test.	Planned	April 2015
Single-center, open-label trial to evaluate the effects of a single 1200 mg IV dose of Orbactiv on the results of multiple coagulation tests in healthy volunteers	The objective of this study is to evaluate the magnitude and duration of any false prolongation of the PT test in healthy volunteers following a single 1200 mg oritavancin infusion.	The magnitude and duration of any false prolongation of the PT test.	Planned	May 2015

Studies which are a condition of the marketing authorisation

None of the above studies is a condition to 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 02-2015.