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Summary of the risk management plan (RMP) for Xydalba (dalbavacin)

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

Overview of disease epidemiology

Xydalba is a medicine 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 it 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

Xydalba contains the active substance dalbavancin, which is a type of antibiotic called glycopeptide. It was compared with vancomycin (another glycopeptide) or with linezolid (an antibiotic that can be taken by mouth) in three main studies involving a total of around 2,000 patients with serious infections of the skin and soft tissue under the skin, such as cellulitis, skin abscesses and wound infections. These also included infections caused by MRSA.

Patients who received vancomycin and responded to treatment had the option to switch to linezolid after 3 days. In all the studies, the main measure of effectiveness was the number of patients whose infection was cured after treatment.

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Xydalba was at least as effective as vancomycin or linezolid at curing the infection. In the 3 studies, between 87% and 94% of patients treated with Xydalba were cured, compared with between 91% and 93% of patients treated with any of the two comparators.

Unknowns relating to treatment benefits

Xydalba has not been studied in children, though a paediatric programme is planned. There are insufficient data in pregnant and breastfeeding women to recommend using Xydalba unless the benefits clearly outweigh the risks.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Development of drug resistance (when the bacteria become resistant to treatment with the medicine)	For the main bacterium causing most of the complicated skin infection (called *Staphyloccus aureus*) only very few strains have been found that are already resistant to the class of antibiotics to which Xydalba belongs. It seems that they do not become easily resistant.	Emergence of resistance can be slowed, but not prevented entirely. It is important to use antibiotics only when needed, to use appropriate doses, to treat for long enough to kill the bacteria, and to choose the right antibiotic for the bacterial infection being treated. Doctors are therefore advised to consider official guidance on the appropriate use of antibiotics when considering prescribing Xydalba.
Pseudomembranous colitis (inflammation of the colon causing severe diarrhoea)	Pseudomembranous colitis is caused by bacteria (*Clostridium difficile*) that produce toxic substances called toxins that cause diarrhoea. This infection can develop following treatment with antibiotics including Xydalba, which kills the normal gut bacteria allowing *Clostridium difficile* to grow. Pseudomembranous colitis has been reported with use of almost all antibiotics and can be severe. In the Xydalba clinical programme, pseudomembranous colitis was uncommon (affecting less than 1 patient in 100).	Ensuring that antibiotics are only used when necessary will limit cases of pseudomembranous colitis. The spread of the bacteria causing pseudomembranous colitis can be reduced with careful handwashing and isolation of infected patients. If pseudomembranous colitis develops doctors should consider stopping Xydalba and using supportive measures.
Hypersensitivity (allergy)	Many antibiotics can cause allergic reactions especially rashes. Women may be more likely to get allergic rashes than men, though age may also play a role. For the class of	Xydalba should be given with caution in patients with a known allergy to a glycopeptide. If an allergic reaction with Xydalba occurs, treatment should be stopped and appropriate therapy for the

Risk	What is known	Preventability
	antibiotics (the so-called glycopeptides) that includes Xydalba, allergic reactions are usually mild, and only rarely severe and life threatening; patients who had an allergic reaction following a glycopeptide other than Xydalba are likely to also be allergic to Xydalba (this is referred to as cross-sensitivity).	allergic reaction should be given.

Important potential risks

Risk	What is known
Hepatic disorder (liver problems)	Liver problems are considered a potential risk because liver abnormalities were seen in animal studies where dalbavancin levels in the blood were more than 6 times higher than human levels. In the Xydalba studies the proportion of patients with abnormal liver function after treatment was 24.4% in Xydalba-treated patients and 25.9% in vancomycin/linezolid-treated patients. Patients who already had an abnormal liver function test before the study had liver-related side effects more often than patients with no liver problems.
Otovestibular toxicity (problems affecting hearing and balance)	The glycopeptides vancomycin and teicoplanin are known to cause hearing problems, especially when given together with antibiotics called aminoglycosides, or in patients with kidney problems. In the Xydalba clinical programme, complete hearing testing was performed in people in early clinical studies, including 10 people with kidney problems and showed no evidence of hearing problems. There were only few patients who were receiving either Xydalba or vancomycin together with aminoglycosides, and they did not report any problems with hearing loss or tinnitus.
Nephrotoxicity (kidney problems)	The glycopeptides teicoplanin and vancomycin are known to cause kidney problems, especially when given together with aminoglycosides. Although no effects on kidney function were seen with Xydalba in human studies, animal studies did show a decrease when dalbavacin blood levels were twice those seen in humans.
Haematologic (blood) effects	Increases or decreases in blood cell counts are commonly seen with severe infections. Some antibiotics have also produced such effects on blood cells especially when given for long periods. Animal studies did not show such an effect with Xydalba and anaemia (low red blood cell counts) was uncommon in human studies.
Use of Xydalba other than the approved use (off-label use)	There is a risk that Xydalba may be prescribed to patients in whom its use is not approved, such as those with bone and joint infections. There is also a risk that Xydalba may be used at doses higher than currently studied, such as a

Risk	What is known
	single (higher) dose or for a period longer than 2 weeks. Information on how well Xydalba works in these circumstances or what side effects could be seen is not available. Xydalba has not yet been fully studied in children, so any use in children is considered off label.

Missing information

Risk	What is known
Use in immunocompromised patients (patients with a weakened immune system)	Clinical trials with Xydalba did not include patients with a weakened immune system (such as those with low white blood cells or severe HIV infection, or patients treated with high doses of corticosteroids). There is no information on efficacy and safety in these patients.
Use in patients with moderate and severe hepatic (liver) impairment	Clinical trials with Xydalba included only few patients with a poorly functioning liver. Therefore there is only little information on the efficacy and safety in these patients and on the appropriate dosing in these patients.
Use in patients with kidney disease with a creatinine clearance (CrCl) of <30 ml/min receiving haemodialysis	One of the clinical trials with Xydalba included patients who were on haemodialysis (because of a poorly functioning kidney). Since the number of patients was small, information on the safety of Xydalba in patients requiring haemodialysis is limited.
Paediatric use (use in children)	Experience in the paediatric population is limited to a 10 patient study including children aged 12-16 years that specifically compared Xydalba blood levels among children of different weights, and between the children and adults. Dose recommendations cannot be made without further information. Any paediatric use is considered off label because a safe, effective dose is not known.
Use in pregnant and breastfeeding women	There are no clinical data in pregnant and breastfeeding women. Therefore, Xydalba should not be used during pregnancy and breastfeeding unless clearly necessary, i.e. if the potential benefit outweighs the possible risk to the fetus.

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 Xydalba can be found on Xydalba'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
In vitro susceptibility surveillance studies with dalbavancin (surveillance programmes)	To monitor for the post-marketing occurrence of resistance to dalbavancin, including resistance patterns and trends.	Occurrence of resistance to dalbavancin.	Planned	Yearly reports to be supplied by laboratories conducting surveillance activities which the company will submit to health authorities.

Studies which are a condition of the marketing authorisation

The above study is not 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.