PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF THE RISK MANAGEMENT PLAN FOR XYDALBA (DALBAVANCIN)

This is a summary of the Risk Management Plan (RMP) for Xydalba. The RMP details important risks of Xydalba, how these risks can be minimised, and how more information will be obtained about Xydalba's risks and uncertainties (missing information). Xydalba's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Xydalba should be used.

This summary of the RMP for Xydalba should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, which are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Xydalba's RMP.

I The medicine and what it is used for

Current:

Xydalba is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults (see the SmPC for the full indication). It contains dalbavancin as the active substance and it is given by intravenous use.

Proposed:

Xydalba is indicated for the treatment of ABSSSI in adults and paediatric patients aged 3 months and older.

Further information about the evaluation of Xydalba's benefits can be found in Xydalba's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to the EPAR summary landing page.

II Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Xydalba, together with measures to minimise such risks and the proposed studies for learning more about Xydalba's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size - the amount of medicine in a pack is chosen to ensure that the medicine is used correctly
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without a prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures. In addition to these measures, information about adverse reactions is collected continuously and is regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Xydalba is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Xydalba are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Xydalba. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 46- Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	Emergence of resistance Pseudomembranous colitis Hypersensitivity
Important potential risks	Hepatic disorder Otovestibular toxicity Nephrotoxicity Haematologic effects
Missing information	Use in immunocompromised patients Use in patients with moderate and severe hepatic

	impairment Use in patients with a CrCl<30 ml/min receiving haemodialysis Paediatric use Use in pregnant and lactating women

II.B Summary of important risks

Table 47- Summary of Important Risks

Important Identified risk: Emergence of resistance	
Evidence for linking the risk to the medicine	Module 2.5 Clinical Overview Module 5, Section 5.3.4.3.1 Summary of Microbiology Programme Scientific literature
Risk factors and risk groups	Hospitalised patients and persons living in institutions, such as long-term care facilities, are at risk for skin infections caused by selected bacterial pathogens resistant to antimicrobials, especially where hygiene habits (e.g. thorough hand washing, changing gowns and gloves) are insufficient. Adherence to infection control procedures is essential to the control of antimicrobial resistance spread in these settings. (WHO, 2002; Larson et al, 2007)
Risk minimisation measures	Routine RMMs only
Important Identified Risk: Pseudomembranous colitis	
Evidence for linking the risk to the medicine	Module 2.4 Non-clinical Overview; Module 2.7.4 Summary of Clinical Safety. Scientific literature
Risk factors and risk groups	In addition to the use of antimicrobials, certain host and environmental factors predispose patients to *C. difficile* colitis. Factors such as advanced age, renal

	insufficiency, ICU admission, severity of underlying disease, as well as setting (inpatient versus outpatient) and duration of hospitalisation play a role in developing CDAD. (Adams and Mercer, 2007; Thielman and Wilson, 2005)
Risk minimisation measures	Routine RMMs only
Important Identified Risk: Hypersensitivity	
Evidence for linking the risk to the medicine	Module 2.4 Nonclinical Overview Module 2.5 Clinical Overview Module 2.7.4 Summary of Clinical Safety Scientific literature
Risk factors and risk groups	Risk factors that place a person at an increased risk for an adverse cutaneous drug reaction include the offending medication, concomitant medications, underlying diseases and the severity of such conditions. (Demoly and Gomes, 2005) The prevalence of adverse cutaneous drug reactions shows that women are more affected than men, although gender differences may depend on the age group. (Demoly and Gomes, 2005)
Risk minimisation measures	Routine RMMs only
Important Potential Risk: Hepatic disorder	
Evidence for linking the risk to the medicine	Module 2.4 Non-clinical Overview Module 2.5 Clinical Overview Module 2.7.4 Summary of Clinical Safety Scientific literature
Risk factors and risk groups	Patients may be at risk for hepatobiliary events due to underlying illness or concomitant medications (e.g., parenteral nutrition, analgesics, lipid lowering agents)

	or alcohol/IV drug abuse. Severe group A streptococcal infection, including cellulitis, has been associated with liver function test abnormalities. Patients with diabetes mellitus are at increased risk of liver injury due to the high burden of non-alcoholic fatty liver disease. (Clark, 2006) Hepatobiliary AEs were reported in clinical trials more frequently in patients who had elevated baseline hepatobiliary values than those who did not. Increased risk for hepatobiliary disorder was not associated with any of the standard demographic variables (age, gender or ethnicity). No dose adjustment of dalbavancin is recommended for patients with mild hepatic insufficiency. In the absence of data to support a dosing recommendation for patients with moderate or severe hepatic insufficiency, caution should be exercised when prescribing dalbavancin to such patients.
Risk minimisation measures	Routine RMMs only
Important Potential Risk: Otovestibular toxicity	
Evidence for linking the risk to the medicine	Scientific literature
Risk factors and risk groups	Occupational exposure to noise can be a significant hazard to one's hearing and it is often reported that the most common cause of hearing problems precipitating tinnitus is exposure to noise. Medications are frequently associated with permanent or temporary tinnitus. Age and underlying diseases or conditions, such as ear infection, allergies, head and neck trauma, are other factors associated with tinnitus. (Henry et al, 2005) Concomitant administration with ototoxic agents (such as NSAIDs, aminoglycosides, amphotericin B, diuretics, chemotherapy or narcotic analgesics) may be a risk factor. (Cianfrone, 2011)

	It has been postulated that vancomycin may affect the auditory system in a manner that results in augmentation of the usual ototoxicity of aminoglycoside antibiotics. (Brummett, 1993) In Phase 2/3 integrated dalbavancin clinical studies, adverse events in patients who received concomitant administration of aminoglycosides were evaluated. No adverse events associated with ear or labyrinth disorders were reported in either dalbavancin-treated or comparator-treated patients. Renal dysfunction has been reported as a risk factor for ototoxicity (Brummett and Morrison, 1990). Complete audiology testing was performed in subjects in Phase 1 clinical studies and included 10 subjects with mild to moderate renal impairment. Results of the audiology assessment indicate no evidence of ototoxicity. Ototoxicity data was also collected in paediatric Study DUR001-106. Two AEs of abnormal acoustic simulation tests (one in cohort 2 y – 6 y and one in cohort 6 y - 11 y) and two AEs of abnormal audiograms (one in cohort 3 mo – 2 y and one in cohort 2 y – 6 y) were reported. All four events were non serious and assessed as not related/unlikely related to study drug. Three events were mild and one was moderate in severity. One event was confounded by cystic fibrosis and a history of chronic aminoglycoside use. One event for abnormal acoustic simulation test was recovered/resolved and the remaining events were reported with an outcome of unknown. In general audiology testing was difficult to perform and interpret in this subject population. Difficulties included lack of cooperation due to age and underlying illness. Despite these limitations, there was no evidence of ototoxicity in a majority of subjects (21/34, 62%); for the remainder no determination could be made, as 2 were lost to follow-up, 4 were uncooperative, 4 needed additional

	testing or had missing raw data results, 2 had distortion product otoacoustic emissions data that was difficult to interpret without additional testing, and 1 had a history confounded by chronic aminoglycoside use. In addition, the risk of ototoxicity in the children under 1 year is a potential risk. Audiologic testing has been conducted in a total of 18 children in Study DUR001-306 (1 in the birth to <3-months cohort; 6 in the 2-year to < 6-year cohort; 4 in the 6-year to < 12-year cohort; 7 in the 12-year to 17-year cohort). Review of the audiology parameters at baseline and Day 28 in all tested subjects (overall and by age cohort) showed no evident signal of ototoxicity and test results at Day 28 remained within the clinically normal range. No bone conduction tests needed to be performed.
Risk minimisation measures	Routine RMMs only
Important Potential Risk: Nephrotoxicity	
Evidence for linking the risk to the medicine	Module 2.7.4 Summary of Clinical Safety Module 2.4 Nonclinical Overview Module 2.5 Clinical Overview Scientific literature
Risk factors and risk groups	Nephrotoxicity may be associated with concurrently administered nephrotoxic drugs, such as NSAIDs, antibiotics such as aminoglycosides, beta lactams or quinolones, ACE inhibitors, diuretics, PPIs, contrast dye, or chemotherapy. The clinical information obtained on concomitant drug therapy during dalbavancin treatment does not indicate any significant drug-drug interactions, but future examinations of concomitant treatments with drugs that are nephrotoxic (and/or ototoxic) is warranted.

Risk minimisation measures	Routine RMMs only
Important Potential Risk: Haematologic effects	
Evidence for linking the risk to the medicine	Module 2.5 Clinical Overview Scientific literature

Risk factors and risk groups	Acute anaemia has a bimodal frequency distribution, affecting mostly young adults and persons in their late fifties. Causes among young adults include trauma, menstrual and ectopic bleeding, and problems of acute haemolysis. During their childbearing years, women are more likely to become iron deficient. In people aged 50-65 years, acute anaemia is usually the result of acute blood loss in addition to a chronic anemic state. This is the case in uterine and GI bleeding. Neoplasia increases in prevalence with each decade of life and can produce anaemia from bleeding, from the invasion of bone marrow with tumour, or from the development of anaemia associated with chronic disorders. Infectious aetiologies of anaemia include viral (hepatitis, infectious mononucleosis, cytomegalovirus), bacterial (Clostridia, gram-negative sepsis) and protozoal (malaria, leishmaniasis, toxoplasmosis) infections, as well as chronic infections in general. (Maakaron, 2013) Patients concurrently receiving other medications associated with leukopenia including neutropenia could be at higher risk. Numerous drugs have been associated with neutropenia, cytotoxic chemotherapy in particular. Other drugs in the highest risk categories are antithyroid medications, macrolides, and procainamides. Other antimicrobials associated with neutropenia include penicillin, cephalosporins, vancomycin, chloramphenicol, gentamicin, clindamycin, doxycycline, flucytosine, nitrofurantoin, novobiocin, minocycline, griseofulvin, lincomycin, metronidazole, rifampin, isoniazid, streptomycin, thiacetazone, mebendazole, pyrimethamine, levamisole, ristocetin, sulfonamides, chloroquine, hydroxychloroquine, quinacrine, ethambutol, dapsone, ciprofloxacin, trimethoprim, imipenem/cilastatin, zidovudine, fludarabine, acyclovir, and terbinafine. (Godwin, 2014) Medications known to cause thrombocytopenia include heparin, platelet glycoprotein (gp) IIb/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban), quinine, quinidine, sulfonamides (sulfa drugs), sulfalike drugs, chlorothiazide, chloroquine, rifampicin and gold salts. (Eke, 2014)

Risk minimisation measures	Routine RMMs only
Missing Information: Use in immunocompromised patients	
Evidence for linking the risk to the medicine	These patients were excluded from the clinical development program in order to assess the safety and efficacy profile in the intended patient population without the confounder of immunosuppression. Infections in immunocompromised patients are likely to be more severe, with more associated complications and potential confounders due to concomitant chemotherapy and underlying disorder. In addition, these patients are likely to be treated in secondary or tertiary centres with higher risk of exposure to multi-drug resistant organisms.
Anticipated risk/consequence of the missing information	Immunocompromised patients might present with infections caused by organisms that would not be pathogenic in healthy individuals, and therefore might have a different microbiological profile compared with those affecting the populations studied in clinical trials; therefore, the benefit profile in this population might not be as well characterized. Population followed up for further characterization: Patients with evidence of significant immunologic disease determined by the following: an absolute neutrophil count of less than 500/mm^3, patients receiving chronic immunosuppressive drugs, and patients with known or suspected HIV with CD4 counts less than 200/uL (or with a past or current AIDS-definining condition and unknown CD4 count). Routine pharmacovigilance surveillance of lack of efficacy and off label use can be used to identify immunocompromised patients who have reduced benefits from treatment with dalbavancin.
Risk minimisation measures	Routine RMMs only

Missing Information: Use in patients with moderate and severe hepatic impairment	
Evidence for linking the risk to the medicine	Patients with known bilirubin >2x the upper limit of normal were excluded in the Vicuron Phase 2/3 clinical trial program. These patients were allowed in the Durata Phase 3 studies, DUR001-301/302/303, and pharmacokinetic studies were conducted in patients with hepatic impairment. No dose adjustment of dalbavancin is recommended for patients with mild hepatic impairment (Child Pugh A). Caution should be exercised when prescribing dalbavancin to patients with moderate or severe hepatic impairment (Child Pugh B & C), as no data are available to determine appropriate dosing (SmPC sections 4.2, 5.2).
Anticipated risk/consequence of the missing information	The efficacy and safety has not been established in patients with moderate or severe hepatic impairment (Child-Pugh B & C). Thus, a potential consequence may be unpredictable pharmacokinetics, underdosing or overdosing. Population followed up for further characterisation: Patients with moderate and severe hepatic impairment.
Risk minimisation measures	Routine RMMs only
Missing Information: Use in patients with a CrCl<30 ml/min receiving haemodialysis	
Evidence for linking the risk to the medicine	Patients with known CrCl ≤50 ml/min were excluded in the Vicuron Phase 2/3 clinical trial program; these patients were allowed in the Durata Phase 3 studies, DUR001-301/302/303, and pharmacokinetic studies were conducted in renally impaired and dialysis patients. Dose adjustment is recommended for patients with chronic renal failure if their CrCl <30 mL/min and they are not receiving regularly scheduled renal dialysis. (SmPC Sections 4.2, 5.2).

Anticipated risk/consequence of the missing information	The efficacy and safety has not been established in this population. Thus, a potential consequence may be unpredictable pharmacokinetics, underdosing or overdosing. Population followed up for further characterisation: Patients with a CrCl<30 ml/min receiving haemodialysis
Risk minimisation measures	Routine RMMs only
Missing Information: Paediatric use	
Evidence for linking the risk to the medicine	Children less than 18 years of age were not included in the adult clinical programme with the exception of two 16 year old subjects who were enrolled in VER001-4 trial. A paediatric investigation plan was agreed with the PDCO to assess ABSSSI in paediatrics prior to obtaining the marketing authorization in Europe and the paediatric investigations are ongoing. Ten adolescents age 12 to 16 years old were enrolled in the PK study A8841004, and 34 patients age 3 months to 11 years old were enrolled in study DUR001-106. Eight patients (neonates to infants < 3 months) with suspected or confirmed bacterial infection were enrolled in PK study DAL-PK-02. A total of 198 patients with ABSSSI from birth to age < 18 years old were enrolled in Study DUR001-306. Overall in Study DUR001-306, a low proportion of subjects experienced a TEAE (8.9% of subjects in dalbavancin single-dose arm, 9.0% of subjects in the dalbavancin two-dose arm, and 3.3% of subjects in the comparator arm). There were no treatment-related SAEs, no treatment related TEAEs, no TEAEs leading to discontinuation of study intervention or study, and no SAEs leading to death in the dalbavancin single-dose or 2-dose arms. Most TEAEs were mild or moderate in severity. There was no notable difference in safety across age cohorts.

	Overall safety findings from the DAL-PK-02, A8841004, and DUR001-106 studies were consistent with that reported for DUR001-306. The safety and efficacy of dalbavancin for the treatment of ABSSSI has been established in paediatric patients aged from 3 months to less than 18 years. Use of dalbavancin for this indication is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data from paediatric patients. The recommended dose of dalbavancin in paediatric patients with ABSSSI with creatinine clearance of 30 ml/min/1.73m^2 and above is a single-dose regimen based on the age and weight of the paediatric patient, administered as a single infusion. The safety and efficacy of dalbavancin in children aged < 3 months old have not yet been established, therefore, no recommendation on a posology can be made.
Anticipated risk/consequence of the missing information	Paediatric patients might be treated empirically by paediatricians. Thus, underdosing with risk of inadequate treatment of the underlying infection, or overdosing is possible. Population followed up for further characterisation: Paediatric patients
Risk minimisation measures	Routine RMMs only
Missing Information: Use in Pregnant and Lactating Women	
Evidence for linking the risk to the medicine	Dalbavancin was not studied in pregnant or lactating women. No treatment-related malformations or embryo-fetal toxicity were observed in pregnant rats or rabbits at clinically relevant exposures of dalbavancin.

	Treatment of pregnant rats with dalbavancin at 3.5 times the human dose on an exposure basis during early embryonic development and from implantation to the end of lactation resulted in delayed fetal maturation and increased fetal loss, respectively. Dalbavancin is not recommended during pregnancy, unless the expected benefit clearly justifies the potential risk to the foetus. Dalbavancin is excreted in the milk of lactating rats. It is not known whether dalbavancin or its metabolite is excreted in human milk; therefore, caution should be exercised when dalbavancin is administered to a nursing woman.
Anticipated risk/consequence of the missing information	Possible impact on the foetus, such as developmental or congenital abnormalities. Possible impact on the pregnancy such as early miscarriage. Population followed up for further characterisation: Pregnant women treated with dalbavancin.
Risk minimisation measures	Routine RMMs only

II.C Post-authorisation development plan

II.C.1 Studies that are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Xydalba.

II.C.2 Other studies in the post-authorisation development plan

Table 48- Studies in post authorisation development plan.

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
In vitro surveillance to monitor any changes in susceptibility of key label pathogens for five years post approval in the US as part of a PMR. Study also includes isolates collected from medical centers in Europe. Category 3	To identify any key pathogens that have developed resistance to dalbavancin and characterize the mechanism(s) of resistance	Surveillance program to monitor the occurrence of resistance to dalbavancin (if any).	Complete	5-year study supplied by laboratories conducting surveillance activities. Yearly reports to be submitted to authorities and to be released in the public domain. Surveillance program results presented and published on a yearly basis in major Infectious Disease Congresses and Journals.