XYDALBA

PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Xydalba

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains dalbavancin hydrochloride equivalent to 500 mg dalbavancin.

After reconstitution each ml contains 20 mg dalbavancin.

The diluted solution for infusion must have a final concentration of 1 to 5 mg/ml dalbavancin (see section 6.6).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion
White to off-white to pale yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xydalba is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and paediatric patients from birth (see sections 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults
The recommended dose of dalbavancin is 1,500 mg administered as either a single infusion of 1,500 mg or as 1,000 mg followed one week later by 500 mg (see sections 5.1 and 5.2).

Paediatric patients
The recommended dose of dalbavancin is a single dose based on the age and weight of the patient.

Dose of dalbavancin in paediatric patients

Age range	Dose (single dose regimen)
Birth to less than 6 years	22.5 mg/kg (maximum 1 500 mg)
6 to less than 18 years	18 mg/kg (maximum 1 500 mg)

Special population
Elderly
No dose adjustment is necessary (see section 5.2).

Renal impairment
Dose adjustments are not required for adult and paediatric patients with mild or moderate renal impairment (creatinine clearance ≥ 30 to 79 ml/min). Dose adjustments are not required for patients receiving regularly scheduled haemodialysis (3 times/week), and dalbavancin may be administered without regard to the timing of haemodialysis.

In adult patients with chronic renal impairment whose creatinine clearance is < 30 ml/min and who are not receiving regularly scheduled haemodialysis, the recommended dose is reduced to either 1,000 mg administered as a single infusion or 750 mg followed one week later by 375 mg (see section 5.2).
There is insufficient information to recommend dosage adjustment for patients 3 months to 18 years with creatinine clearance less than 30 ml/min/1.73 m^2 and for patients < 3 months old with renal impairment defined as serum creatinine ≥ 2 times the upper limit of normal, or urine output < 0.5 mL/kg/h, or requirement for dialysis. Currently available information is described in section 5.2, but no recommendation on a posology can be made.

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 (see sections 5.2).

Method of administration

Intravenous use

Xydalba must be reconstituted and then further diluted prior to administration by intravenous infusion over a 30 - minute period. For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Dalbavancin should be administered with caution in patients known to be hypersensitive to other glycopeptides since cross-hypersensitivity may occur. If an allergic reaction to dalbavancin occurs, administration should be discontinued and appropriate therapy for the allergic reaction should be instituted.

Clostridioides (formerly *Clostridium*) *difficile*-associated diarrhoea

Antibacterial-associated colitis and pseudomembranous colitis have been reported with the use of nearly all antibiotics and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the treatment with dalbavancin (see section 4.8). In such circumstance, the discontinuation of dalbavancin and the use of supportive measures together with the administration of specific treatment for *Clostridioides* (formerly *Clostridium*) *difficile* should be considered. These patients must never be treated with medicinal products that suppress the peristalsis.

Infusion-related reactions

Xydalba is to be administered via intravenous infusion, using a total infusion time of 30 minutes to minimise the risk of infusion-related reactions. Rapid intravenous infusions of glycopeptide antibacterial agents can cause reactions, including flushing of the upper body, urticaria, pruritus, and/or rash. Stopping or slowing the infusion may result in cessation of these reactions.

Renal impairment

Information on the efficacy and safety of dalbavancin in patients with creatinine clearance < 30 ml/min is limited. Based on simulations, dose adjustment is needed for adult patients with chronic renal impairment whose creatinine clearance is < 30 ml/min and who are not receiving regular haemodialysis (see sections 4.2 and 5.2). There is insufficient information to recommend dosage adjustment for patients 3 months to 18 years old with creatinine clearance less than 30 ml/min/1.73 m^2 and for patients < 3 months old with renal impairment defined as serum creatinine ≥ 2 times the upper limit of normal, or urine output < 0.5 mL/kg/h, or requirement for dialysis.

Mixed infections

In mixed infections in which Gram-negative bacteria are suspected patients should also be treated with an appropriate antibacterial agent(s) against Gram-negative bacteria (see section 5.1**)**.

Non-susceptible organisms

The use of antibiotics may promote the overgrowth of non-susceptible micro-organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Limitations of the clinical data

There is limited data on safety and efficacy of dalbavancin when administered for more than two doses (one week apart). In the major trials in ABSSSI the types of infections treated were confined to cellulitis/erysipelas, abscesses and wound infections only. There is no experience

with dalbavancin in the treatment of severely immunocompromised patients.

4.5 Interaction with other medicinal products and other forms of interaction

Results from an *in vitro* receptor screening study do not indicate a likely interaction with other therapeutic targets or a potential for clinically relevant pharmacodynamic interactions (see section 5.1).

Clinical drug-drug interaction studies with dalbavancin have not been conducted.

Potential for other medicinal products to affect the pharmacokinetics of dalbavancin.

Dalbavancin is not metabolised by CYP enzymes *in vitro*, therefore co-administered CYP inducers or inhibitors are unlikely to influence the pharmacokinetics of dalbavancin.

It is not known if dalbavancin is a substrate for hepatic uptake and efflux transporters. Co-administration with inhibitors of these transporters may increase the exposure to dalbavancin. Examples of such transporter inhibitors are boosted protease inhibitors, verapamil, quinidine, itraconazole, clarithromycin and cyclosporine.

Potential for dalbavancin to affect the pharmacokinetics of other medicinal products.

The interaction potential of dalbavancin on medicinal products metabolised by CYP enzymes is expected to be low since it is neither an inhibitor nor an inducer of CYP enzymes *in vitro*. There are no data on dalbavancin as an inhibitor of CYP2C8.

It is not known if dalbavancin is an inhibitor of transporters. Increased exposure to transporter substrates sensitive for inhibited transporter activity, such as statins and digoxin, cannot be excluded if combined with dalbavancin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of dalbavancin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Xydalba is not recommended during pregnancy, unless the potential expected benefit clearly justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether dalbavancin is excreted in human milk. However, dalbavancin is excreted in the milk of lactating rats and may be excreted in human breast milk. Dalbavancin is not well absorbed orally; however, an impact on the gastrointestinal flora or mouth flora of a breast-feeding infant cannot be excluded. A decision must be made whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Xydalba taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Studies in animals have shown reduced fertility (see section 5.3). The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

Xydalba may have a minor influence on the ability to drive and use machines, as dizziness has been reported in a small number of patients (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In Phase 2 / 3 clinical studies, 2,473 adult patients received dalbavancin administered as either a single infusion of 1,500 mg or as 1,000 mg followed one week later by 500 mg. The most common adverse reactions occurring in ≥ 1 % of patients treated with dalbavancin were nausea (2.4 %), diarrhoea (1.9 %), and headache (1.3 %) and were generally of mild or moderate severity.

Tabulated list of adverse reactions (Table 1)

The following adverse reactions have been identified in Phase 2/3 clinical trials with dalbavancin. Adverse reactions are classified according to System Organ Class and frequency. Frequency categories are derived according to the following conventions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000).

Table 1

System Organ Class	Common	Uncommon	Rare
Infections and infestations		vulvovaginal mycotic infection, urinary tract infection, fungal infection, *Clostridioides* (formerly *Clostridium*) *difficile* colitis, oral candidiasis	
Blood and lymphatic system disorders		anaemia, thrombocytosis, eosinophilia, leucopenia, neutropenia	
Immune system disorders			anaphylactoid reaction
Metabolism and nutrition disorders		decreased appetite	
Psychiatric disorders		Insomnia	
Nervous system disorders	headache	dysgeusia, dizziness	
Vascular disorders		flushing, phlebitis	
Respiratory, thoracic and mediastinal disorders		Cough	bronchospasm
Gastrointestinal disorders	nausea, diarrhoea,	constipation, abdominal pain, dyspepsia, abdominal discomfort, vomiting	
Skin and subcutaneous		pruritus, urticaria, rash	

System Organ Class	Common	Uncommon	Rare
tissue disorders			
Reproductive system and breast disorders		vulvovaginal pruritus	
General disorders and administration site conditions		infusion-related reactions	
Investigations		blood lactate dehydrogenase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood uric acid increased, liver function test abnormal, transaminases increased, blood alkaline phosphatase increased, platelet count increased, body temperature increased, hepatic enzyme increased, gamma-glutamyl transferase increased,	

Description of selected adverse reactions

Class adverse reactions
Ototoxicity has been associated with glycopeptide use (vancomycin and teicoplanin); patients who are receiving concomitant therapy with an ototoxic medicinal product, such as an aminoglycoside, may be at increased risk.

Paediatric population

The safety of dalbavancin was evaluated in one Phase 3 clinical trial which included 169 paediatric patients from birth to less than 18 years of age with ABSSSI (or suspected or confirmed sepsis if aged less than 3 months old) treated with dalbavancin (91 patients treated with a single dose of dalbavancin and 78 patients, all of them aged 3 months and older, treated with a two-dose regimen of dalbavancin). Out of these 169 paediatric patients, 58 were adolescents (12 years and older), 49 were children from 6 years to less than 12 years, 35 were 2 years to less than 6 years, 17 were aged 3 months to less than 2 years, and 10 were under 3 months of age. Additionally, in a Phase 1, open-label, pharmacokinetic trial, a single-dose administration of dalbavancin was evaluated in 8 patients under 3 months of age. Across these two clinical studies, 18 children were under 3 months of age, including 3 preterm and 5 term neonates. Overall, the safety findings of dalbavancin in these paediatric patients were similar to those observed in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il
In addition, you may report suspected adverse reactions by sending an e-mail message to safety@tzamal-medical.co.il

4.9 Overdose

No specific information is available on the treatment of overdose with dalbavancin, as dose-limiting toxicity has not been observed in clinical studies. In Phase 1 studies, healthy volunteers have been administered single doses of up to 1,500 mg, and cumulative doses up to 4,500 mg over a period of up to 8 weeks, with no signs of toxicity or laboratory results of clinical concern. In Phase 3 studies, patients have been administered single doses of up to 1,500 mg.

Treatment of overdose with dalbavancin should consist of observation and general supportive measures. Although no information is available specifically regarding the use of haemodialysis to treat overdose, it should be noted that in a Phase 1 study in patients with renal impairment, less than 6 % of the recommended dalbavancin dose was removed after 3 hours of haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, glycopeptide antibacterials, ATC code: J01XA04.

Mechanism of action

Dalbavancin is a bactericidal lipoglycopeptide.

Its mechanism of action in susceptible Gram-positive bacteria involves interruption of cell wall synthesis by binding to the terminal D-alanyl-D-alanine of the stem peptide in nascent cell wall peptidoglycan, preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits resulting in bacterial cell death.

Mechanism of resistance

All Gram-negative bacteria are inherently resistant to dalbavancin.

Resistance to dalbavancin in *Staphylococcus* spp. and *Enterococcus* spp. is mediated by VanA, a genotype that results in modification of the target peptide in nascent cell wall. Based on *in vitro* studies the activity of dalbavancin is not affected by other classes of vancomycin resistance genes.

Dalbavancin MICs are higher for vancomycin-intermediate staphylococci (VISA) than for fully vancomycin susceptible strains. If the isolates with higher dalbavancin MICs represent stable phenotypes and are correlated with resistance to the other glycopeptides, then the likely mechanism would be an increase in the number of glycopeptide targets in nascent peptidoglycan.

Cross-resistance between dalbavancin and other classes of antibiotics was not seen in *in vitro* studies. Methicillin resistance has no impact on dalbavancin activity.

Interactions with other antibacterial agents

In *in vitro* studies, no antagonism has been observed between dalbavancin and other

commonly used antibiotics (i.e. cefepime, ceftazidime, ceftriaxone, imipenem, meropenem, amikacin, aztreonam, ciprofloxacin, piperacillin/tazobactam and trimethoprim/sulfamethoxazole), when tested against 12 species of Gram-negative pathogens (see section 4.5).

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretative criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for dalbavancin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

PK/PD relationship

Bactericidal activity against staphylococci *in vitro* is time-dependent at serum concentrations of dalbavancin similar to those obtained at the recommended dose in humans. *In vivo* PK/PD relationship of dalbavancin for *S. aureus* was investigated using a neutropenic model of animal infection. This showed that the antibacterial activity of dalbavancin appears to best correlate with the ratio of area under the unbound plasma concentration-time curve to minimal inhibitory concentration (*f*AUC/MIC).

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the pathogens listed for ABSSSI that were susceptible to dalbavancin *in vitro:*

- *Staphylococcus aureus,*
- *Streptococcus pyogenes,*
- *Streptococcus agalactiae,*
- *Streptococcus dysgalactiae,*
- *Streptococcus anginosus group (*includes *S. anginosus, S. intermedius,* and *S. constellatus).*

Antibacterial activity against other relevant pathogens

Clinical efficacy has not been established against the following pathogens although *in vitro* studies suggest that they would be susceptible to dalbavancin in the absence of acquired mechanisms of resistance:

- Group G streptococci
- *Clostridium perfringens*
- *Peptostreptococcus* spp.

Paediatric population

Xydalba has been evaluated in paediatric patients aged from birth to < 18 years with ABSSSI or suspected or confirmed sepsis if aged less than 3 months old in one Phase 3 open-label, randomised, comparator controlled clinical trial. The study included 169 patients treated with dalbavancin (91 patients treated with a single dose of dalbavancin and 78 patients, all of them aged 3 months and older, treated with a two-dose regimen of dalbavancin) and 30 patients treated with comparator. Seven of 10 patients aged less than 3 months were enrolled with suspected or confirmed sepsis. The primary objective was to assess the safety and tolerability of dalbavancinand secondary objectives included assessment of efficacy and pharmacokinetics. Efficacy was a descriptive endpoint. Clinical cure rate at TOC (mITT) was 95.2 % (79/83) in the dalbavancinsingle-dose arm, 97.3 % (72/74) in the dalbavancintwo-dose arm and 100 % (30/30) in the comparator arm.

5.2 Pharmacokinetic properties

The pharmacokinetics of dalbavancin have been characterised in healthy subjects, patients, and special populations. Systemic exposures to dalbavancin are dose proportional following single doses over a range of 140 to 1120 mg, indicating linear pharmacokinetics of dalbavancin. No accumulation of dalbavancin was observed following multiple intravenous infusions administered once-weekly for up to 8 weeks (1,000 mg on Day 1, followed by up to 7 weekly 500 mg doses) in healthy adults.

The mean terminal elimination half-life ($t_{1/2}$) was 372 (range 333 to 405) hours. The pharmacokinetics of dalbavancin are best described using a three-compartment model (α and β distributional phases followed by a terminal elimination phase). Thus, the distributional half-life ($t_{1/2\beta}$), which constitutes most of the clinically-relevant concentration-time profile, ranged from 5 to 7 days and is consistent with once-weekly dosing.

Estimated pharmacokinetic parameters of dalbavancin following the two-dose regimen and the single-dose regimen, respectively, are shown in Table 2 below.

Table 2

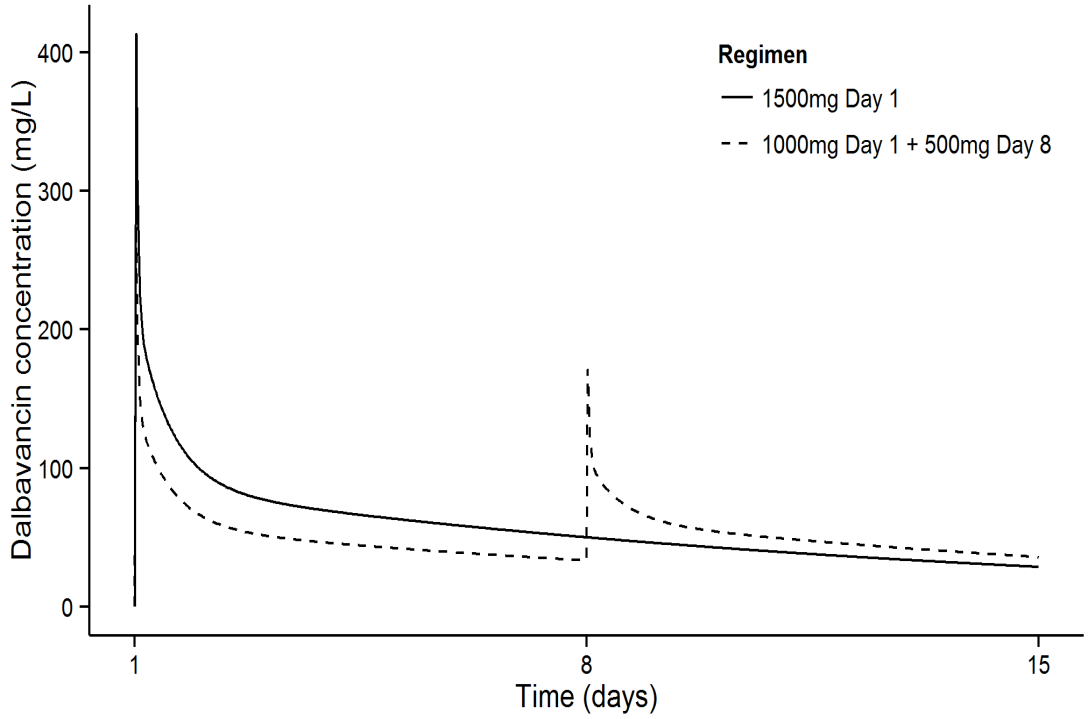
Mean (SD) dalbavancin pharmacokinetic parameters for adults using population PK analysis[1]

Parameter	Two-dose regimen[2]	Single-dose regimen[3]
C_{max} (mg/L)	Day 1: 281 (52) Day 8: 141 (26)	Day 1: 411 (86)
$AUC_{0\text{-Day}14}$ (mg•h/L)	18100 (4600)	20300 (5300)
CL (L/h)	0.048 (0.0086)	0.049 (0.0096)

[1] Source: DAL-MS-01.
[2] 1,000 mg on Day 1 + 500 mg on Day 8; Study DUR001-303 subjects with evaluable PK sample.
[3] 1,500 mg; Study DUR001-303 subjects with evaluable PK sample.

The dalbavancin plasma concentration-time following the two-dose and the single-dose regimens, respectively, are shown in Figure 1.

Figure 1. Dalbavancin Plasma Concentrations versus time in a typical adult ABSSSI patient (simulation using population pharmacokinetic model) for both the single and the two-dose regimens.



Distribution

Clearance and volume of distribution at steady state are comparable between healthy subjects and patients with infections. The volume of distribution at steady state was similar to the volume of extracellular fluid. Dalbavancin is reversibly bound to human plasma proteins, primarily to albumin. The plasma protein binding of dalbavancin is 93 % and is not altered as a function of drug concentration, renal insufficiency, or hepatic insufficiency. Following a single intravenous dose of 1,000 mg in healthy volunteers AUC in skin blister fluid amounted (bound and unbound dalbavancin) to approximately 60 % of the plasma AUC at day 7 post-dose.

Biotransformation

Metabolites have not been observed in significant amounts in human plasma. The metabolites hydroxy-dalbavancin and mannosyl aglycone have been detected in urine (< 25 % of administered dose). The metabolic pathways responsible for producing these metabolites have not been identified; however, due to the relatively minor contribution of metabolism to the overall elimination of dalbavancin, drug-drug interactions via inhibition or induction of metabolism of dalbavancin are not anticipated. Hydroxy-dalbavancin and mannosyl aglycone show significantly less antibacterial activity compared to dalbavancin.

Elimination

Following administration of a single 1,000 mg dose in healthy subjects, an average of 19 % to 33 % of the administered dalbavancin dose was excreted in urine as dalbavancin and 8 % to 12 % as the metabolite hydroxy-dalbavancin. Approximately 20 % of the administered dose was excreted in faeces.

Special populations

Renal impairment

The pharmacokinetics of dalbavancin were evaluated in 28 subjects with varying degrees of renal impairment and in 15 matched control subjects with normal renal function. Following a single dose of 500 mg or 1,000 mg dalbavancin, the mean plasma clearance (CL_T) was reduced 11 %, 35 %, and 47 % in subjects with mild (CL_{CR} 50 - 79 ml/min), moderate (CL_{CR} 30 – 49 ml/min), and severe (CL_{CR} < 30 ml/min) renal impairment, respectively, compared to subjects with normal renal function. The mean AUC for subjects with creatinine clearance < 30 ml/min was approximately 2 - fold higher. The clinical significance of the decrease in mean plasma CL_T, and the associated increase in AUC0-∞ noted in these pharmacokinetic studies of dalbavancin in subjects with severe renal impairment has not been established. Dalbavancin pharmacokinetics in subjects with end-stage renal disease receiving regularly scheduled renal dialysis (3 times/week) were similar to those observed in subjects with mild to moderate renal impairment, and less than 6 % of an administered dose is removed after 3 hours of haemodialysis. For dosing instructions in subjects with renal impairment refer to section 4.2.

There is insufficient information to recommend dose adjustment for patients 3 months to 18 years with creatinine clearance less than 30 mL/min/1.73 m^2. Patients < 3 months old with renal impairment, defined as serum creatinine ≥ 2 times the upper limit of normal, or urine output < 0.5 mL/kg/h, or requirement for dialysis, were excluded from the clinical trials. For the 18 paediatric patients < 3 months old that were included in the clinical trials, the range of normalised creatinine clearance (based on Schwartz bedside equation) was 34 to 118 mL/min/1.73 m^2 No observed PK data are available in paediatric patients with severe renal impairment. The predicted dalbavancin mean AUC for paediatric subjects with severe renal impairment (CL_{CR} ≤ 30 ml/min/1.73 m^2) was approximately 13-30 % higher compared to paediatric patients with normal renal function treated with the same dose, based on population pharmacokinetic modelling.

Hepatic impairment

The pharmacokinetics of dalbavancin were evaluated in 17 subjects with mild, moderate, or severe hepatic impairment and compared to 9 matched healthy subjects with normal hepatic function. The mean AUC was unchanged in subjects with mild hepatic impairment compared to subjects with normal hepatic function; however, the mean AUC decreased by 28 % and 31 %, respectively, in subjects with moderate and severe hepatic impairment. The cause and the clinical significance of the decreased exposure in subjects with moderate and severe hepatic function are unknown. For dosing instructions in subjects with hepatic impairment refer to section 4.2.

Gender

Clinically significant gender-related differences in dalbavancin pharmacokinetics have not been observed in healthy subjects or in patients with infections. No dose adjustment is recommended based on gender.

Elderly

The pharmacokinetics of dalbavancin were not significantly altered with age; therefore, dose adjustment is not necessary based on age (see section 4.2). The experience with dalbavancin

in elderly is limited: 276 patients ≥ 75 years of age were included in the Phase 2/3 clinical studies, of which 173 received dalbavancin. Patients up to 93 years of age have been included in clinical studies.

Paediatric population
The pharmacokinetics of dalbavancin has been evaluated in 219 paediatric patients [4 days to 17 years of age, including preterm neonates (gestational age 32 to <37 weeks; n=3) and term neonates (gestational age 37 to 40 weeks; n=5)]. The model predicted mean plasma $AUC_{0\text{-}120h}$ of dalbavancin in preterm neonates at birth (gestational age 32 weeks to <37 weeks) was approximately 62% of that in adult patients, whereas the $AUC_{0\text{-}120h}$ in older paediatric groups was 84-96% of that in adult patients. However, in all paediatric age groups, the percentage of patients attaining the PK/PD targets related to the *in vivo* drug activity were above 90% for MICs up to 0.5 mg/L.

Table 3.
Simulated Mean (SD) dalbavancin pharmacokinetic parameters for paediatrics and adults using population PK analysis[1]

Parameter	Preterm Neonate	Term Neonate	Young Infant	Infant	Toddler	Child	Adolescent	Adult
Age range	GA 26--<37 weeks	Birth -1 month	1 month - < 3 months	3 months - <2 years	2 years - < 6 years	6 years - < 12 years	12 years - < 18 years	> = 18 years
Dose	22.5 mg/kg	22.5 mg/kg	22.5 mg/kg	22.5 mg/kg	22.5 mg/kg	18 mg/kg	18 mg/kg	1500 mg
C_{max} (mg/L)	228 (88)	305 (130)	305 (130)	306 (130)	303 (130)	258 (110)	250 (110)	417 (110)
$AUC_{0\text{-}120h}$ (mg•h/L)	6480 (2000)	8930 (2900)	9040 (3000)	9470 (3100)	10100 (3300)	8850 (2900)	9030 (3100)	10500 (3100)

[1] Source: DAL-MS-03.

5.3 Preclinical safety data

Dalbavancin toxicity has been evaluated after daily intravenous administration for durations of up to 3 months in rats and dogs. Dose-dependent toxicity included serum chemistry and histological evidence of renal and hepatic injury, reduced red blood cell parameters and injection site irritation. In dogs only, infusion reactions characterised by skin swelling and/or redness (not associated with the injection site), mucosal pallor, salivation, vomiting, sedation, and modest declines in blood pressure and increases in heart rate were observed in a dose-dependent manner. These infusion reactions were transient (resolved within 1 hour post-dosing) and were attributed to histamine release. Dalbavancin toxicity profile in juvenile rats was consistent with that previously observed in adult rats at the same dose (mg/kg /day) levels.

Reproductive toxicity studies in rats and rabbits showed no evidence of a teratogenic effect. In rats, at exposures approximately 3 times above clinical exposure, there was reduced fertility and an increased incidence of embryo-lethality, reductions in foetal weight and skeletal ossification and increased neonatal mortality. In rabbits, abortion occurred in conjunction with maternal toxicity at exposures below the human therapeutic range.

Long-term carcinogenicity studies have not been conducted. Dalbavancin was not mutagenic or clastogenic in a battery of *in vitro* and *in vivo* genotoxicity tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Lactose monohydrate
Water for injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or intravenous solutions other than those mentioned in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Chemical and physical in-use stability of Xydalba has been demonstrated for both the reconstituted concentrate and for the diluted solution for 48 hours at or below 25 °C. The total in-use stability from reconstitution to administration should not exceed 48 hours.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions. Do not freeze.

6.4 Special precautions for storage

Dry powder: store below 25 °C.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Single-use 48 ml type I glass vial with a gray rubber stopper and a green flip off seal.

Each pack contains 1 vial.

6.6 Special precautions for disposal and other handling

Xydalba must be reconstituted with 25 ml sterile water for injections and subsequently diluted with 50 mg/ml (5 %) glucose solution for infusion.

Xydalba vials are for single-use only.

Instructions for reconstitution and dilution

Aseptic technique must be used for reconstitution and dilution of Xydalba.

1. The content of each vial must be reconstituted by slowly adding 25 ml of sterile water for injections.
2. **Do not shake.** To avoid foaming, alternate between gentle swirling and inversion of the vial, until its contents are completely dissolved. The reconstitution time may be up to 5 minutes.
3. The reconstituted concentrate in the vial contains 20 mg/ml dalbavancin.
4. The reconstituted concentrate must be a clear, colourless to yellow solution with no visible particles.
5. The reconstituted concentrate must be further diluted with 50 mg/ml (5 %) glucose solution for infusion.
6. To dilute the reconstituted concentrate, the appropriate volume of the 20 mg / ml concentrate must be transferred from the vial to an intravenous bag or bottle containing 50 mg/ml (5 %) glucose solution for infusion. For example: 25 ml of the concentrate contains 500 mg dalbavancin.
7. After dilution the solution for infusion must have a final concentration of 1 to 5 mg/ml dalbavancin
8. The solution for infusion must be clear, colourless to yellow solution with no visible particles.
9. If particulate matter or discoloration is identified, the solution must be discarded.

Xydalba must not be mixed with other medicinal products or intravenous solutions. Sodium chloride containing solutions can cause precipitation and should NOT be used for reconstitution or dilution. The compatibility of reconstituted Xydalba concentrate has only been established with 50 mg/ml (5 %) glucose solution for infusion.

If a common intravenous line is being used to administer other medicinal products in addition to Xydalba, the line should be flushed before and after each Xydalba infusion with 5% glucose solution for infusion.

Use in the paediatric population

For paediatric patients, the dose of Xydalba will vary according to the age and weight of the child up to a maximum of 1,500 mg. Transfer the required dose of reconstituted dalbavancin solution, according to the instructions above, based on the child's weight, from the vial to an intravenous bag or bottle containing 50 mg/ml (5 %) glucose solution for infusion. The diluted solution must have a final dalbavancin concentration of 1 to 5 mg/ml.

Table 4 below provides information to prepare an infusion solution with a final concentration of 2 mg/ml or 5 mg/ml (sufficient for most scenarios), to be administered by syringe pump, to achieve a dose of 22.5 mg/kg in paediatric patients from birth to 12 months of age weighing from 3 to 12 kg. Alternative concentrations may be prepared, but must have a final concentration range of 1 to 5 mg/ml of dalbavancin. Refer to Table 4 to confirm the calculations. Values shown are approximate. Note that the table is NOT inclusive of all possible calculated doses for every age group but may be utilised to estimate the approximate volume to verify the calculation.

Table 4. Preparation of Xydalba (final infusion concentration 2 mg/ml or 5 mg/ml to be administered by syringe pump) in paediatric patients from birth to 12 months (22.5 mg/kg dose)

Patient Weight (kg)	Dose (mg) to achieve 22.5 mg/kg	Volume of reconstituted dalbavancin solution (20 mg/ml) to be withdrawn from vial (ml)	Volume of diluent 50 mg/ml (5 %) glucose solution to add for mixing (ml)	Final dalbavancin infusion solution concentration	Total Volume Dosed by syringe pump (ml)
1	22.5	10 ml	90 ml	2 mg/ml	11.3
2	45.0				22.5
3	67.5				33.8
4	90.0				45.0
5	112.5				56.3
6	135.0				67.5
7	157.5				78.8
8	180.0				90.0
9	202.5	20 ml	60 ml	5 mg/ml	40.5
10	225.0				45.0
11	247.5				49.5
12	270.0				54.0

~~Patient Weight (kg)~~	~~Dose (mg) to achieve 22.5 mg/kg~~	~~Volume of reconstituted dalbavancin solution (20 mg/ml) to be withdrawn from vial (ml)~~	~~Volume of diluent 50 mg/ml (5 %) glucose solution to add for mixing (ml)~~	~~Final dalbavancin infusion solution concentration~~	~~Total Volume Dosed by syringe pump (ml)~~
~~3~~	~~67.5~~	~~10 ml~~	~~90 ml~~	~~2 mg/ml~~	~~33.8~~
~~4~~	~~90.0~~				~~45.0~~
~~5~~	~~112.5~~				~~56.3~~
~~6~~	~~135.0~~				~~67.5~~
~~7~~	~~157.5~~				~~78.8~~
~~8~~	~~180.0~~				~~90.0~~
~~9~~	~~202.5~~	~~20 ml~~	~~60 ml~~	~~5 mg/ml~~	~~40.5~~
~~10~~	~~225.0~~				~~45.0~~
~~11~~	~~247.5~~				~~49.5~~
~~12~~	~~270.0~~				~~54.0~~

Disposal

Discard any portion of the reconstituted solution that remains unused.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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8. REGISTRATION HOLDER

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9. REGISTRATION NUMBER :

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