

BSAC OPAT Workshop

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***Where does dalbavancin fit within my  
hospital?***

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# Disclosures

Advisory Board attendance / presentations delivered / chairing duties / sponsorship for meeting attendance:

*Astellas, AZ, Bayer, Cardiome, Eumedica, Luminex, MSD, Novartis, Pall, Pfizer, Proeconomy*

N.B. Access given to Cardiome medical slide set for this presentation; all views expressed are entirely my own

# Dalbavancin

- Dalbavancin is a second generation lipoglycopeptide bactericidal antibiotic against susceptible Gram-positive pathogens
- Has a pharmacokinetic profile allowing either single or two dose (once-weekly) intravenous regimen



**Xydalba ▼ (dalbavancin) is a PRESCRIPTION ONLY MEDICINE.**

Xydalba 500 mg powder for concentrate for solution for infusion.

Adverse events should also be reported to: Cardiome UK Ltd –

Tel: +44 (0)203 002 8114; email: [medinfo@cardiome.com](mailto:medinfo@cardiome.com)

The full SmPC is available at the Cardiome Stand.

Cardiome Pharma Corp | Correvio (UK) Ltd

Lakeside House

Furzeground Way

Stockley Park

Uxbridge

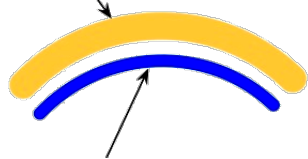
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# Mechanism of action:

Interferes with cell wall synthesis and causes bacterial death

Gram-positive

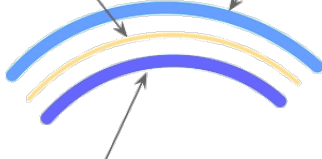
Peptidoglycan



Membrane

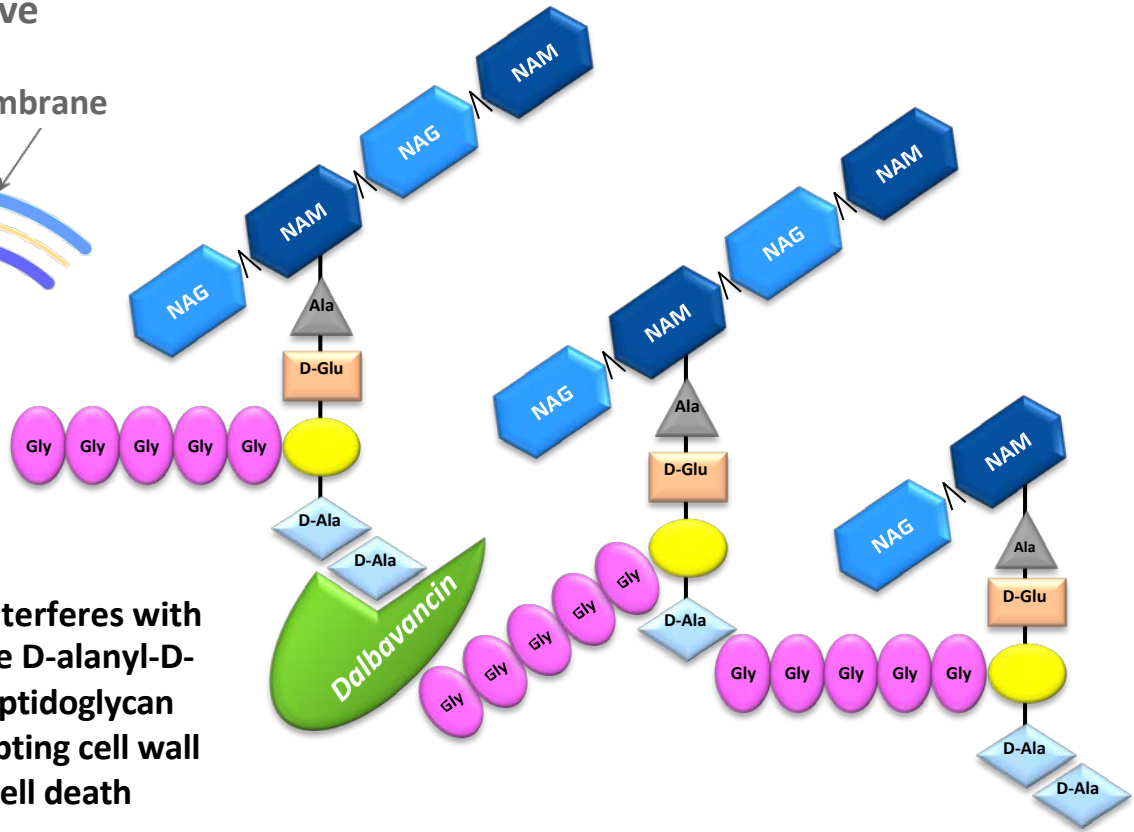
Gram-negative

Outer membrane  
Peptidoglycan



membrane

Dalbavancin, like other glycopeptides, interferes with the cell wall formation by binding to the D-alanyl-D-alanine (D-ala-D-ala) terminus of the peptidoglycan preventing cross linking, thereby interrupting cell wall synthesis and resulting in bacterial cell death



# Efficacy against specific pathogens

## Gram-positive pathogens

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**Demonstrated Clinical Efficacy** 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*).

***In vitro* Efficacy** (in absence of acquired mechanisms of resistance)

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

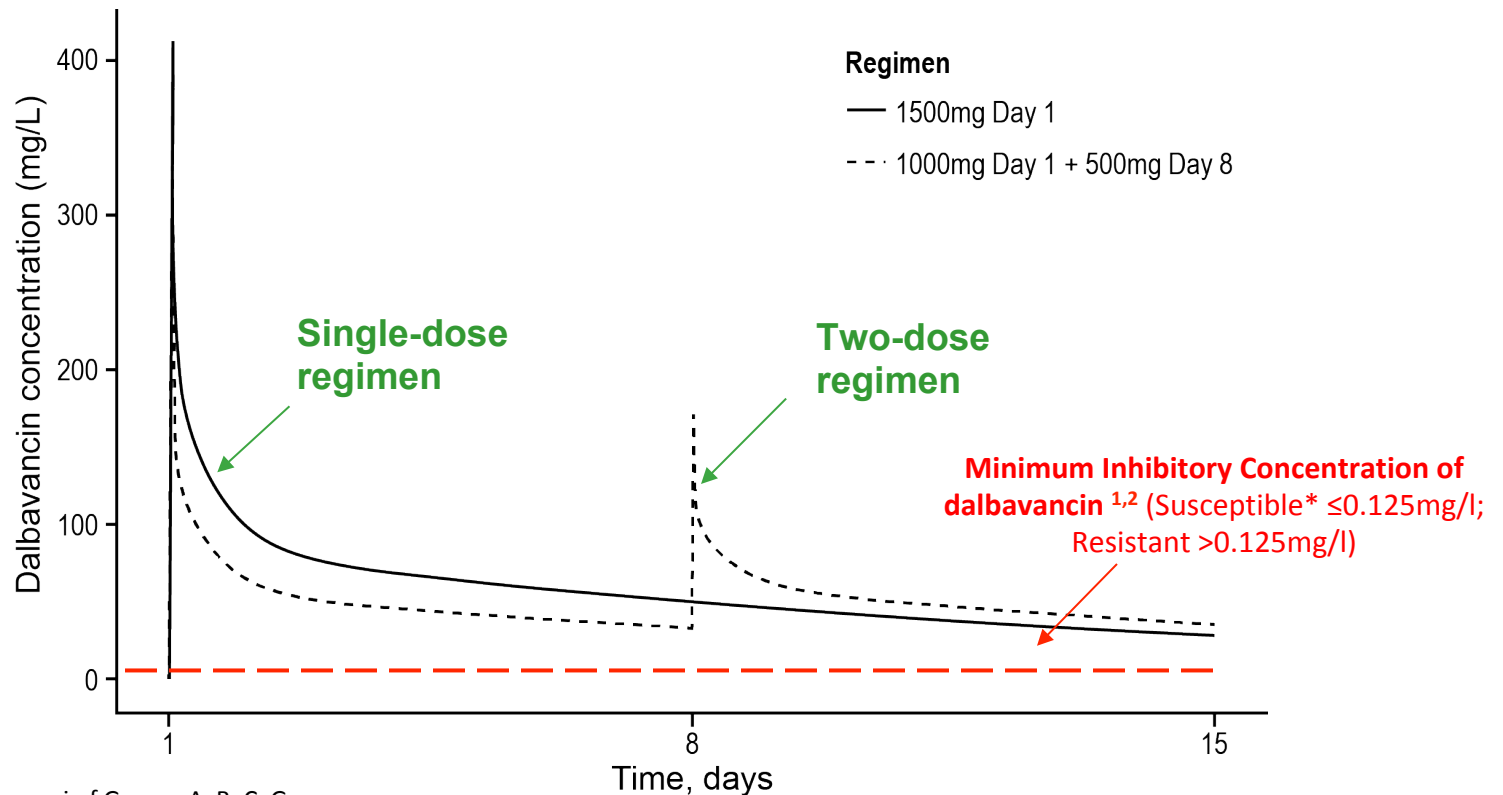
# Comparative *in vitro* activity of dalbavancin against 39,824 Isolates of *S. aureus* from the US (2002–2012)

Antimicrobial Agent	MIC, µg/mL			% resistant <sup>a</sup>
	50%	90%	Range	EUCAST
Dalbavancin	0.06	0.06	≤0.03 - 0.5	—
Vancomycin	1	1	≤0.12 - 4	<0.1
Teicoplanin	≤2	≤2	≤2 - 8	0.3
Oxacillin	>2	>2	≤0.25->2	52.5
Erythromycin	>2	>2	≤0.2 - >2	63.5
Clindamycin	≤0.25	>2	≤0.25 - >2	23.5
Daptomycin	0.25	0.5	≤0.12 - 4	0.1
Levofloxacin	≤0.5	>4	≤0.5 - >4	42.3
Linezolid	1	2	≤0.25 - >8	<0.1
Tetracycline	≤4	≤4	≤4 - >8	9.9

<sup>a</sup> Criteria as published by EUCAST 2013 ; Data from R. Jones, JMI Laboratories, SENTRY database.

# Pharmacokinetics: One and two-dose regimen of dalbavancin

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



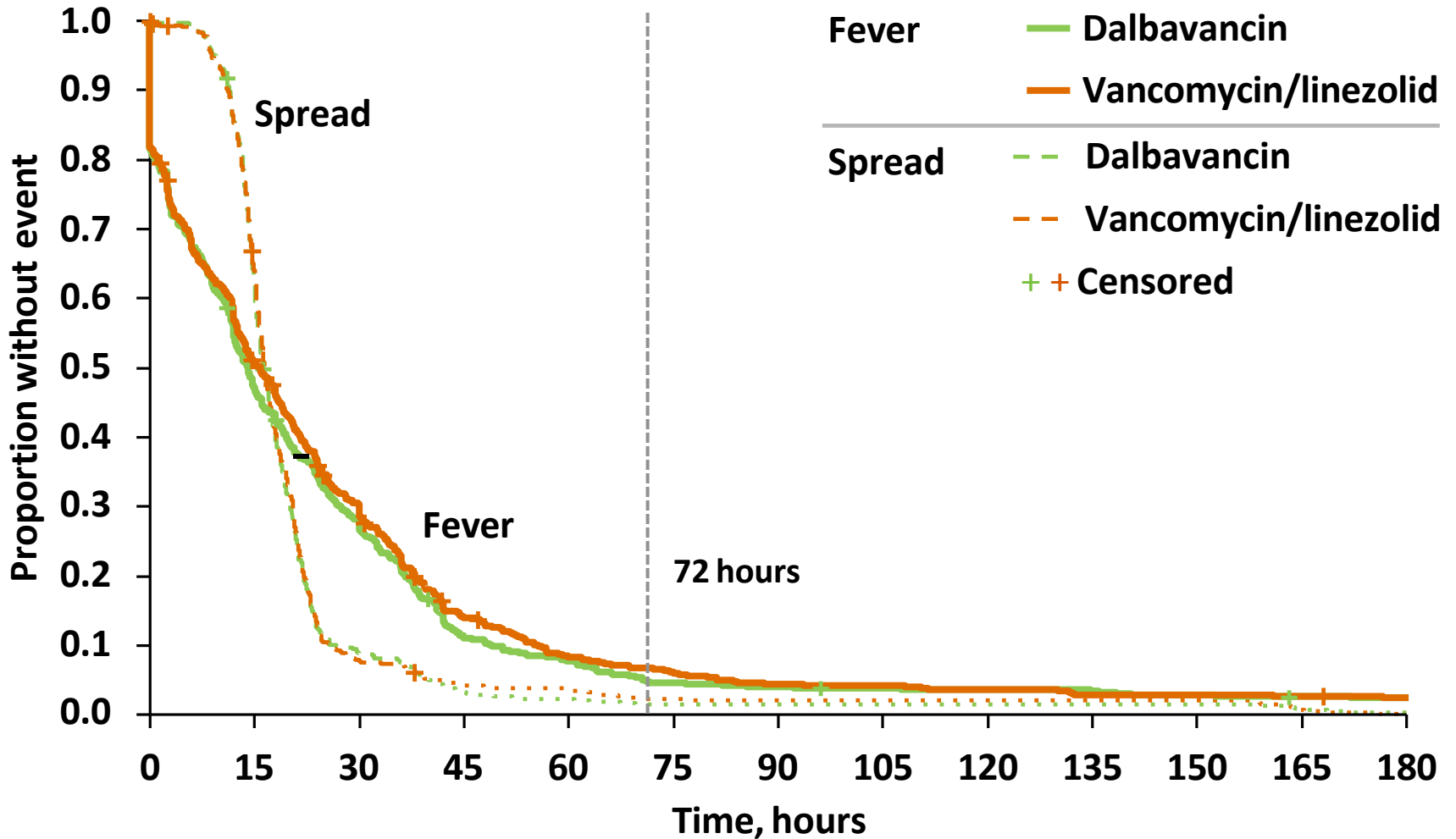
Determined by EUCAST;

\*Staphylococcus spp.

\* Beta-haemolytic streptococci of Groups A, B, C, G

\* Viridans group streptococci (Streptococcus anginosus group only)

# Time to absence of fever or cessation of spread



# Adverse Reactions having occurred in >1% of Patients\* - All Phase 2/3 trials

Most common adverse reactions in Phase 2/3 Studies in $\geq 1\%$ of Patients Treated With Dalbavancin	n=2,473
Nausea	2.4%
Diarrhoea	1.9%
Headache	1.3%

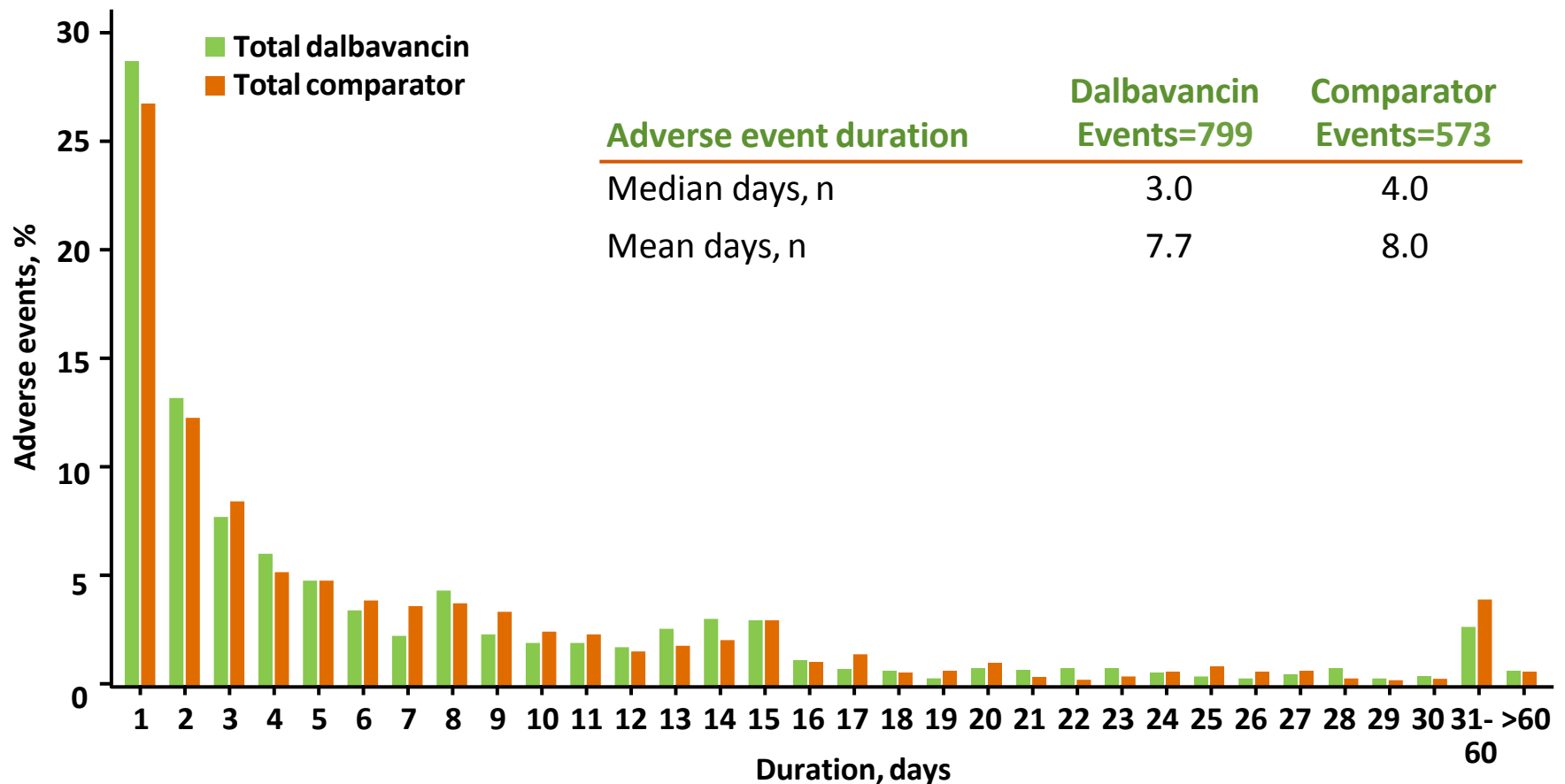
- In Phase 2/3 clinical studies, 2,473 patients received Dalbavancin administered as either a single infusion of 1500 mg or as 1000 mg followed one week later by 500 mg.
- The most common adverse reactions were generally of mild or moderate severity.

\* Complete Tabulated list of adverse reactions available in SmPC

# Duration of adverse events

## Phase 2/3 trials

The distribution of the duration of adverse events in patients receiving dalbavancin was similar to that on the comparator regimens



# Dosing in special populations

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## No recommended dosage adjustment for:

- ✓ Elderly
- ✓ Gender
- ✓ Mild Hepatic Impairment\*
- ✓ Mild or moderate renal impairment ( $\text{CrCl} \geq 30$  ml/min).
- ✓ Severe renal Impairment with regular haemodialysis (3x/week), administration without regard to timing of haemodialysis

## Dose reduction for :

- Chronic renal Impairment with  $\text{CrCl} < 30$  ml/min and without regular scheduled haemodialysis
  - 1000 mg as single infusion or 750 mg on Day 1 and 375 mg on Day 8

\* Caution should be exercised when prescribing XYDALBA to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) as no data are available to determine the appropriate dosing in these patients.

# Low potential for drug interactions

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- **Dalbavancin has a low potential for drug-drug interactions\***
  - Dalbavancin is not a substrate, inducer, or inhibitor of cytochrome P450 isoenzymes *in vitro*
  - 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.
  - No antagonism between dalbavancin and 12 commonly used antibiotics against 12 species of Gram-negative pathogens in *in vitro studies*
    - cefepime, ceftazidime, ceftriaxone, imipenem, meropenem, amikacin, aztreonam, ciprofloxacin, piperacillin/tazobactam and trimethoprim/sulfamethoxazole

\*Clinical drug-drug interaction studies with XYDALBA have not been conducted.

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

# How we use dalbavancin

- Position in therapy

# WUTH Dalbavancin D&T Application

- Use for moderate to severe ABSSSI when OPAT unsuitable or at capacity
- Safety valve for A&E

*With*

- Appropriate patient selection
- Appropriate antimicrobial stewardship
- Governance in place

# IV line issues

- Potential for misuse - IVDU
- Concern if poor home environment
- Patient compliance with line care
- Dermatological conditions: risk of line infection / bacteraemia

# Patient centred care

OPAT may not be suitable due to:

- Work limitations
- Travel
- Carer / young families
- Students
- Needle phobia

# Dalbavancin governance

- Establish 'gatekeeper' roles
- Patient selection – severity of infection (moderate to severe ABSSSI)
- Duration of IV treatment at least 1 week
- Choice of regimen – single dose or two-dose regimen
- Clarity re clinical responsibility / follow up arrangements

# Abbreviated Prescribing Information

- **Refer to the Summary of Product Characteristics before prescribing.**
- **PRESCRIPTION ONLY MEDICINE.**
- **Product name:** Xydalba 500 mg powder for concentrate for solution for infusion.
- **Presentation:** Each vial contains dalbavancin hydrochloride equivalent to 500 mg dalbavancin.
- **Therapeutic indications:** Xydalba is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
- **Posology:** *Recommended dose and duration of treatment for adults:* The recommended dose of dalbavancin in adult patients with ABSSSI is 1500 mg administered as either a single infusion of 1500 mg or as 1000 mg followed one week later by 500 mg. **Elderly:** No dose adjustment is necessary. **Gender:** No dose adjustment is recommended based on gender. **Renal impairment:** Dose adjustments are not required for patients with mild or moderate renal impairment (creatinine clearance  $\geq$  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 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 1000 mg administered as a single infusion or 750 mg followed one week later by 375 mg. **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. **Paediatric population:** The safety and efficacy of dalbavancin in children aged from birth to  $<$  18 years has not yet been established.
- **Method of administration:** *Intravenous use:* Xydalba must be reconstituted and then further diluted prior to administration by intravenous infusion over a 30 - minute period.
- **Contraindications:** Hypersensitivity to the active substance or to any of the excipients.
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# Abbreviated Prescribing Information (cont.)

- **Special warnings and precautions for use:** Hypersensitivity reactions: Xydalba should be administered with caution in patients known to be hypersensitive to other glycopeptides since cross-hypersensitivity may occur. If an allergic reaction to Xydalba occurs, administration should be discontinued and appropriate therapy for the allergic reaction should be instituted. 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. In such circumstance, the discontinuation of dalbavancin and the use of supportive measures together with the administration of specific treatment for 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 that resemble “Red-Man Syndrome”, 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 patients with chronic renal impairment whose creatinine clearance is < 30 ml/min and who are not receiving regular haemodialysis. 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. 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.
- **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. 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. 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*. It is not known if dalbavancin is an inhibitor of transporters.
- **Fertility, pregnancy and lactation:** Pregnancy: There are no data from the use of dalbavancin in pregnant women. Studies in animals have shown reproductive toxicity. Xydalba is not recommended during pregnancy unless clearly necessary. 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. 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. The potential risk for humans is unknown.

# Abbreviated Prescribing Information (cont.)

- **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.
- **Undesirable effects:** In Phase 2 / 3 clinical studies, 2,473 patients received dalbavancin administered as either a single infusion of 1500 mg or as 1000 mg followed one week later by 500 mg. The most common adverse reactions occurring in  $\geq 1\%$  of patients treated with dalbavancin were nausea (2.4 %), diarrhoea (1.9 %), and headache (1.3 %) and were generally of mild or moderate severity. The following adverse reactions have been identified in Phase 2/3 clinical trials with dalbavancin. Frequency categories are derived according to the following conventions: common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ). **Common:** headache, nausea, diarrhoea. **Uncommon:** vulvovaginal mycotic infection, urinary tract infection, fungal infection, *Clostridium difficile* colitis, oral candidiasis, anaemia, thrombocytosis, eosinophilia, leucopenia, neutropenia, decreased appetite, insomnia, dysgeusia, dizziness, flushing, phlebitis, cough, constipation, abdominal pain, dyspepsia, abdominal discomfort, vomiting, pruritus, urticaria, rash, vulvovaginal pruritus, infusion-related reactions, 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. **Rare:** anaphylactoid reaction, bronchospasm. **Class adverse reactions:** Ototoxicity has been associated with glycopeptide use (vancomycin and teicoplanin); patients who are receiving concomitant therapy with an ototoxic agent, such as an aminoglycoside, may be at increased risk.
- **Overdose:** No specific information is available on the treatment of overdose with dalbavancin, as dose-limiting toxicity has not been observed in clinical studies. Treatment of overdose with dalbavancin should consist of observation and general supportive measures.
- **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.
- **Paediatric population:** The safety and efficacy of Xydalba in children aged from birth to  $< 18$  years have not yet been established. A total of 10 paediatric patients with ages 12 to 16 years who had resolving infections were given single doses of either dalbavancin 1000 mg (body weight  $\geq 60$  kg) or dalbavancin 15 mg/kg (body weight  $< 60$  kg). Mean plasma exposures for dalbavancin, based on  $AUC_{inf}$  and  $C_{max}$  were similar when administered as 1000 mg to paediatric subjects (12-16 years) weighing  $> 60$  kg or as 15 mg/kg to paediatric subjects weighing  $< 60$  kg. The safety profile of dalbavancin in the subjects aged between 12 and 16 years in this study was consistent with the safety profile observed in adults treated with dalbavancin.

# Abbreviated Prescribing Information (cont.)

- **Incompatibilities:** Sodium chloride solutions may cause precipitation and must not be used for reconstitution or dilution. This medicinal product must not be mixed with other medicinal products or intravenous solutions other than those mentioned below.
- **Shelf life:** Dry powder: 4 years. 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.
- **Special precautions for disposal and other handling:** Xydalba must be reconstituted with 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 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. 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.
- **Packaging, quantity and price (excluding VAT):** Single-use 48 ml type I glass vial with an elastomeric stopper and a green flip off seal. Each pack contains 1 vial. Price: £558.70 per 500mg vial.
- **Marketing authorisation holder:** Allergan Pharmaceuticals International Ltd., Clonsaugh Industrial Estate, Coolock, Dublin 17, Ireland.
- **Marketing authorisation number:** EU/1/14/986/001.
- **Date of revision of the text:** March, 2017.
  - Adverse events should be reported. Reporting forms and information can be found at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)
  - Adverse events should also be reported to: Cardiome UK Ltd (Tel: +44 (0)203 002 8114; email: [medinfo@cardiome.com](mailto:medinfo@cardiome.com))

# Update on dalbavancin activity tested against Gram-positive clinical isolates from 39 European hospitals (2011–13)

Organism (No. tested)	MIC, µg/mL		% inhibited at dalbavancin MIC, µg/mL			
	50%	90%	≤0.03	0.06	0.12	0.25
<i>S. aureus</i> (2861)	0.06	0.06	29.4	91.0	>99.9	100
MSSA (2203)	0.06	0.06	27.1	90.3	100	
MRSA (658)	0.06	0.06	37.1	93.3	99.8	100
Vancomycin MIC ≤ 1 mg/L (642)	0.06	0.06	38.0	94.2	100	
Vancomycin MIC 2 mg/L (16)	0.06	0.12	0.0	56.3	93.8	100
VGS <sup>a</sup> (69)	≤0.03	≤0.03	97.1	98.6	100	
<i>S. anginosus</i> group (48)	≤0.03	≤0.03	100			
BHS <sup>b</sup> (466)	≤0.03	≤0.03	91.0	98.5	100	
<i>S. pyogenes</i> (223)	≤0.03	≤0.03	92.8	98.2	100	
<i>S. agalactiae</i> (135)	≤0.03	0.06	88.9	98.5	100	
<i>S. dysgalactiae</i> (47)	≤0.03	≤0.03	91.5	100		

BHS, β-haemolytic streptococci.

<sup>a</sup> Includes: *S. anginosus* (28 isolates), *S. anginosus* group (5), *Streptococcus bovis* group (2), *Streptococcus constellatus* (14), *Streptococcus intermedius* (1), *Streptococcus mitis/oralis* (4), *S. mitis* group (5), *S. oralis* (5), *Streptococcus parasanguinis* (1), *Streptococcus salivarius* (1), *Streptococcus sanguinis* (1) and unspciated VGS (2).

<sup>b</sup> Includes: *S. agalactiae* (135 isolates), *S. dysgalactiae* (47), *Streptococcus equisimilis* (5), *S. pyogenes* (223), group C streptococci (13), group F streptococci (1) and group G streptococci (42).