

PI & AE Reporting

Please consult the Summary of Product Characteristics (SmPC) for further information including adverse effects.

Each vial contains 500 mg of ceftobiprole (as 666.6 mg ceftobiprole medocartil sodium). After reconstitution, each mL of concentrate contains 50 mg of ceftobiprole (as 66.7 mg of ceftobiprole medocartil sodium). **Therapeutic indications:** Indicated for the treatment of the following infections in neonates, infants, children, adolescents and adults: Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP) Community-acquired pneumonia (CAP) Consideration should be given to official guidance on the appropriate use of antibacterial agents. **Posology:** 500 mg administered as 2-hour intravenous infusion every 8 hours. For CAP, a switch to an appropriate oral antibiotic may be considered after completion of at least 3 days of intravenous ceftobiprole medocartil treatment, depending on the patient's clinical response. **Paediatric Population: The safety and efficacy of Zevtera in preterm neonates have not been established. Zevtera is not recommended for use in preterm neonates. Elderly patients:** No dose adjustment in elderly patients, except in cases of moderate to severe renal impairment. **Renal impairment: No dose adjustment in patients with mild renal impairment (CLCR 50 to 80 mL/min). Dose adjustment is required in patients with moderate (CLCR 30 to <50 mL/min), or severe (CLCR <30mL/min) impaired renal function or end-stage renal disease with or without intermittent haemodialysis. Patients with creatinine clearance >150 mL/min:** In patients with a supra-normal creatinine clearance (>150mL/min), based on pharmacokinetic/pharmacodynamic considerations, prolongation of the infusion duration to 4 hours is recommended. **Hepatic impairment:** No experience in patients with hepatic impairment. However, as ceftobiprole undergoes minimal hepatic metabolism and is eliminated predominantly by kidneys, dose adjustment is not considered necessary. **Method of administration:** Must be reconstituted and then further diluted prior to administration by intravenous infusion over a period of 2 hours. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity to the cephalosporin class of antibacterials. Immediate and severe hypersensitivity (e.g., anaphylactic reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins or carbapenems). **Special warnings and precautions for use:** Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported. In severe hypersensitivity reactions, treatment must be discontinued immediately, and emergency measures must be initiated. Caution should be used if this medicine is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents. Seizures have been associated with the use of this medicine, most commonly in patients with pre-existing central nervous system (CNS)/seizure disorders. *Clostridioides difficile*-associated diarrhoea. Antibacterial agent-associated colitis and pseudomembranous colitis reported use of this medicine and may range from mild to life-threatening. Discontinuation of therapy with this medicine and the administration of specific treatment for *Clostridioides difficile*-associated diarrhoea should be considered. Medicinal products that inhibit peristalsis should not be given. This medicine may result in overgrowth of non-susceptible organisms,

including fungi. Appropriate measures should be taken if evidence of super-infection occurs during therapy. Advisable to correct hypovolaemia to maintain normal urinary output in patients receiving this medicine. Precipitation can occur when this medicine is mixed with calcium-containing solutions in the same intravenous (IV) administration line. No experience with ceftobiprole in the treatment of HAP (excluding VAP) and CAP in HIV-positive patients, patients with neutropenia, immunocompromised patients, and patients with myelosuppression. Caution is advised in these patients. This medicine has not been shown to be effective in the treatment of patients with VAP and should not be initiated in these patients. In patients with HAP who subsequently require ventilation, this medicine should be used with caution. Susceptibility to Enterobacteriaceae. Ceftobiprole, like other cephalosporins is susceptible to hydrolysis that may be produced by Enterobacteriaceae including many of the extended-spectrum beta-lactamases (ESBLs), serine carbapenemases, class B metallo-beta-lactamases (among others). Therefore, information on the prevalence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) should be taken into consideration when selecting treatment **Interaction with other medicinal products:** No clinical interaction studies have been performed. Caution is advised when this medicine is administered together with drugs with narrow therapeutic index. Please refer to SPC for further interactions. **Pregnancy:** This medicine should not be used during pregnancy unless strictly necessary. **Breast-feeding:** Animal studies have shown the excretion of ceftobiprole/metabolites in milk at low concentrations. It is unknown whether ceftobiprole is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. **Side effects: Common:** fungal infections, hyponatraemia, nausea, vomiting, diarrhoea, infusion site reactions, hypersensitivity (including urticaria, pruritic rash and drug hypersensitivity), dysgeusia, headache, dizziness, somnolence, abdominal pain, dyspepsia, Hepatic enzymes increased, Rash. *Less frequently reported but more serious adverse reactions:* thrombocytopenia, agranulocytosis, anaphylaxis, *Clostridioides difficile*, colitis, convulsion, agitation and renal failure. Prescribers should consult the summary of product characteristics in relation to other adverse reactions. **Marketing authorisation holder:** Mercury Pharmaceuticals Limited, Capital House, 1st Floor, 85 King William Street, London, EC4N 7BL, UK or Correvio, 15 rue du Bicentenaire, 92800 Puteaux, France. **Marketing authorisation number(s) UK:** PL 12762/0655, AT: 135392, FR: 3400927731662, ES: 78691, DE: 88776.00.00, IT: 043060019. **Legal Category:** POM. **Last revised:** November 2022. **Date of preparation:** November 2022. (ADV/CEF/PI/0003)

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Please consult the Summary of Product Characteristics (SmPC) for further information including adverse effects (available on: www.ema.europa.eu).

Xydalba™ (dalbavancin hydrochloride) 500 mg powder for concentrate for solution for infusion. **Presentation:** White to off-white to pale yellow powder for concentrate for solution for infusion. Each vial contains dalbavancin hydrochloride equivalent to 500mg dalbavancin. After reconstitution each mL contains 20mg dalbavancin. The diluted solution for infusion must have a final concentration of 1-5mg/mL dalbavancin. **Indication:** For the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. **Dosage and administration: Method of administration:** Intravenous use. **Adults:** 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. **Children and adolescents aged from 6 years to less than 18 years:** The recommended dose of dalbavancin is a single dose of 18 mg/kg (maximum 1,500 mg). **Infants and children aged from 3 months to less than 6 years:** The recommended dose of dalbavancin is a single dose of 22.5 mg/kg (maximum 1,500 mg). **Elderly:** No dose adjustment is necessary. In patients with chronic renal impairment whose creatinine clearance is <30 mL/min and who are not receiving regularly scheduled haemodialysis, reduced dose recommended to either 1,000 mg administered as a single infusion or 750 mg followed one week later by 375 mg. 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. Xydalba must be reconstituted and then further diluted prior to administration by IV infusion over a 30-minute period. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use:** 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. Do not give this medicine to children under 3 months. The use of Xydalba in children under 3 months has not been studied enough. *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. 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: Rapid infusions of glycopeptide 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. Excipient: This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'. **Incompatibilities:** Sodium chloride solutions may cause precipitation and must not be used for reconstitution or dilution. **Interaction:** *In vitro* receptor screening study do not indicate a likely interaction with other therapeutic targets or a potential for clinically relevant pharmacodynamic interactions. Co-administered CYP inducers or inhibitors are unlikely to influence the pharmacokinetics of dalbavancin. Co-administration with inhibitors of hepatic uptake and efflux transporters may increase the exposure to dalbavancin. Examples of such transporter inhibitors are boosted protease inhibitors, verapamil, quinidine, itraconazole, clarithromycin and cyclosporine. Increased exposure to transporter substrates sensitive for inhibited transporter activity, such as statins and digoxin, cannot be excluded if combined with dalbavancin. **Pregnancy and lactation:** Not recommended during pregnancy, unless the potential expected benefit clearly justifies the potential risk to the foetus. Continue/discontinue therapy with Xydalba taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Undesirable effects: Serious:** Anaphylactoid reaction, bronchospasm, *Clostridioides* (formerly *Clostridium*) *difficile* colitis and phlebitis. **Common:** 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. (Please refer to the Summary of Product Characteristics for detailed information). **Overdose:** 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. **Legal category:** POM **Marketing authorisation number:** EU/1/14/986/00. **Marketing authorisation holder:** AbbVie Ltd, Maidenhead, SL6 4UB, UK (Distributed by: ADVANZ PHARMA: Capital House, 1st Floor, 85 King William Street, London EC4N 7BL, UK) **Date of revision:** 08/02/23 (ADV/XYD/PM/0003)

Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Adverse events should also be reported to Advanz Pharma Medical Information via telephone on **+44 208 588 9131** or via e-mail at medicalinformation@advanzpharma.com

For Healthcare Professionals Only

Date of preparation: February 2023 EU/MISC/PM/0001

Zevtera®/Mabelio® is indicated for the treatment of the following infections in term neonates, infants, children, adolescents and adults¹:

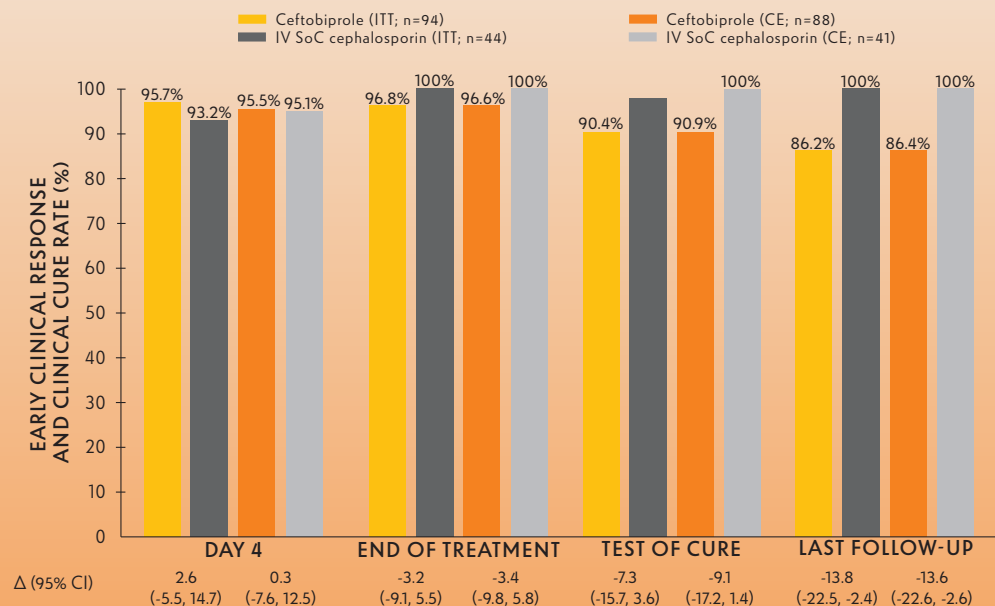
- Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)
- Community-acquired pneumonia (CAP)

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

Efficacy and safety of ceftobiprole demonstrated in paediatric patients²

In a Phase 3, randomized, investigator-blinded trial comparing ceftobiprole with a SoC cephalosporin, with or without vancomycin

Clinical response in CAP and HAP, in children from 3 months to <18 years²



Adapted from Bosheva, et al., 2023²

Xydalba™ is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and paediatric patients aged 3 months and older³. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Efficacy and safety of dalbavancin demonstrated in paediatric patients⁴

In a Phase 3, multicenter, open-label, randomized, comparing dalbavancin with an active comparator

Clinical response* in paediatric patients, all cohorts (mITT** population)⁴

Clinical response, n (%)	Dalbavancin Single-Dose (N = 78)	Dalbavancin 2-dose (N = 78)	Comparator (N = 30)
48-72h	n = 78	n = 74	n = 29
Clinical responder	76 (97.4)	73 (98.6)	26 (89.7)
Clinical non-responder	2 (2.6)	1 (1.4)	3 (10.3)
EOT	n = 77	n = 74	n = 30
Clinical cure	79 (94.8)	68 (91.9)	30 (100)
Improvement	3 (3.9)	4 (5.4)	0
Clinical failure	1 (1.3)	2 (2.7)	0
TOC	n = 76	n = 74	n = 30
Clinical cure	73 (96.1)	72 (97.3)	30 (100)
Clinical failure	1 (1.3)	2 (2.7)	0
Unknown	2 (2.6)	0	0
Follow-up	n = 77	n = 73	n = 30
Clinical cure	75 (97.4)	71 (97.3)	30 (100)
Clinical failure	1 (1.3)	2 (2.7)	0
Unknown	1 (1.3)	0	0

*Sponsor assessment, **mITT: randomized patients who received ≥1 dose of study drug and had a diagnosis of ABSSSI (or, in cohort 5, suspected/confirmed sepsis) not known to be caused exclusively by a Gram-negative organism.

Adapted from Giorgobiani, et al., 2022⁴

[†]Clinical success achieved in 84% of adults patients (ITT) on day 14 in the phase III study assessing a single dose vs two-dose regimen in ABSSSI.⁵ Clinical cure rate similar across dalbavancin Single-Dose (97.4%) and 2-dose regimen (97.3%).⁴

EOT, end of treatment; mITT, modified intent-to-treat; TOC, test of cure; AE, adverse events; ITT, intent-to-treat; TEAE, treatment-emergent adverse events.

Safety in CAP and HAP, in children from 3 months to <18 years²

Patients with ≥ 1 AE, n(%)	While on IV therapy		Overall study duration*	
	Ceftobiprole (N = 94)	IV SoC cephalosporin (N = 44)	Ceftobiprole (N = 94)	IV SoC cephalosporin (N = 44)
Any AE	19 (20.2)	8 (18.2)	30 (31.9)	13 (29.5)
Treatment-related AE	8 (8.5)	0	9 (9.6)	0
Severe AE	1 (1.1)	0	3 (3.2)	0
Treatment-related severe AE	0	0	0	0
Serious AE	2 (2.1)	0	7 (7.4)	2 (4.5)
Treatment-related AE	1 (1.1)	0	1 (1.1)	0
AE leading to treatment discontinuation	4 (4.3)	0	4 (4.3)	0
AE leading to death	0	0	0	0
AEs occurring in ≥3% of either treatment group at any time during the study				
Vomiting	4 (4.3)	1 (2.3)	7 (7.4)	1 (2.3)
Diarrhea	1 (1.1)	4 (9.1)	2 (2.1)	4 (9.1)
Viral infection	2 (2.1)	1 (2.3)	4 (4.3)	1 (2.3)
Headache	3 (3.2)	0	3 (3.2)	0
Pneumonia	1 (1.1)	0	3 (3.2)	0
Bronchitis	0	0	0	2 (4.5)

*Up to the last follow-up visit

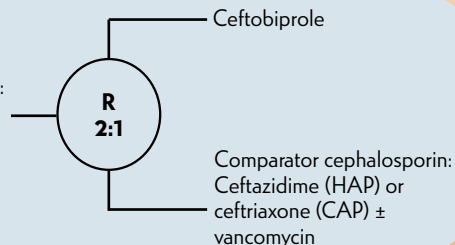
Adapted from Bosheva, et al., 2023²

Study methodology²

Paediatric patients with HAP or CAP requiring hospitalisation (n = 138)

Stratified by HAP or CAP and age group:

- 3 mo to <2 years
- 2 to <6 years
- 6 to <12 years
- 12 to <18 years



Primary endpoint:

- Cumulative incidence of AEs during the first 3 days of study treatment and at EOT, TOC, LFU (safety population)

Secondary endpoints:

- Early clinical response at Day 4
- Clinical cure rates at the EOT, TOC, and LFU visits
- Clinical and microbiologic relapse rates at the LFU visit
- Microbiologic eradication rates at the TOC visit
- Duration of IV antibiotic treatment
- Time to oral antibiotic switch
- Duration of hospitalization

Safety* in paediatric patients⁴

AEs, n(%)	Dalbavancin Single-Dose (N = 83)	Dalbavancin 2-dose (N = 78)	Comparator (N = 30)
Overall AEs	6 (7.2)	8 (10.3)	1 (3.3)
TEAEs	6 (7.2)	7 (9.0)	1 (3.3)
Serious TEAEs	3 (3.6)	0	0
Cohort 1, ages 12 to <18 years	n = 29	n = 29	n = 6
TEAEs	1 (3.4)	2 (6.9)	0
Serious TEAEs	1 (3.4)	0	0
Cohort 2, ages 12 to <18 years	n = 25	n = 24	n = 11
TEAEs	1 (4.0)	0	0
Serious TEAEs	0	0	0
Cohort 3, ages 6 to <12 years	n = 18	n = 17	n = 10
TEAEs	1 (5.6)	1 (5.9)	0
Serious TEAEs	0	0	0
Cohort 4, ages 3 mo. to <2 years	n = 6	n = 8	n = 3
TEAEs	1 (16.7)	4 (50.0)	0
Serious TEAEs	1 (16.7)	0	0
Cohort 5, ages birth to <3 mo.	n = 5	n = 0	n = 0
TEAEs	2 (40.0)	-	-
Serious TEAEs	1 (20.0)	-	-

*All patients in the ITT population who received ≥1 dose of study drug.

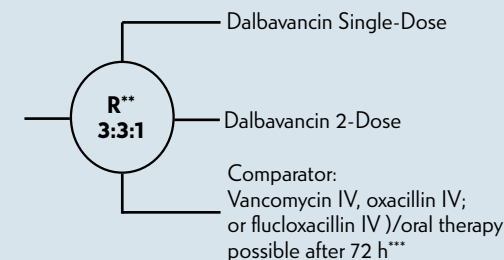
Adapted from Giorgobiani, et al., 2022⁴

Study methodology⁴

Paediatric patients with ABSSSI (n = 191)

Stratified by age group:

- Cohort 1: 12 to 17 years*
- Cohort 2: 6 to <12 years
- Cohort 3: 2 to <6 years
- Cohort 4: 3 mo to <2 years
- Cohort 5: birth to <3mo



*Inclusive; **Patients birth to <3 months old were not included in the randomization scheme and were all assigned to single-dose dalbavancin. ***Possible after ≥72 h from oxacillin or flucloxacillin to oral cefadroxil, or from IV vancomycin to oral clindamycin (for MRSA)

Primary endpoint: Safety and tolerability was evaluated by physical examination (baseline, 48–72 hours, day 8, EOT, TOC, follow-up visit and premature discontinuation); vital signs (every visit); AEs; death, audiology testing (baseline and at TOC) and effect of dalbavancin on bowel flora (from birth to <2 years)

Secondary endpoints: clinical response according to clinical and microbiologic parameters (48–72 hours, EOT and TOC)

[†]Clinical success achieved in 84% of adults patients (ITT) on day 14 in the phase III study assessing a single dose vs two-dose regimen in ABSSSI.⁵ Clinical cure rate similar across dalbavancin Single-Dose (97.4%) and 2-dose regimen (97.3%).⁴

EOT, end of treatment; TOC, test of cure; AE, adverse events; ITT, intent-to-treat; TEAE, treatment-emergent adverse events.

References

1. Zevtera® SmPC
2. Bosheva M, et al. A Phase 3, Randomized, Investigator-blinded Trial Comparing Ceftobiprole With a Standard-of-care Cephalosporin, With or Without Vancomycin, for the Treatment of Pneumonia in Pediatric Patients. *Pediatric Infectious Disease Journal* 2021; 40e222-9
3. Xydalba™ SmPC
4. Giorgobiani M, et al. The Safety and Efficacy of Dalbavancin and Active Comparator in Pediatric Patients With Acute Bacterial Skin and Skin Structure Infections. *Pediatr Infect Dis J* 2022; DOI: 10.1097/INF.0000000000003798

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