swissmedic

Date: 24 January 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Tenkasi

International non-proprietary name: oritavancin

Pharmaceutical form: powder for concentrate for solution for infusion

Dosage strength(s): 400 mg

Route(s) of administration: intravenous use

Marketing authorisation holder: A. Menarini GmbH

Marketing authorisation no.: 68135

Decision and decision date: extension of therapeutic indication approved on 15 November 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ABSSSI	Acute bacterial skin and skin structure infections
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MRSA	Methicillin-resistant *Staphylococcus aureus*
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Tenkasi is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults **and paediatric patients aged 3 months and older** (see "Dosage/Administration", "Warnings and precautions" and "Properties/Effects") if it is established or strongly suspected after microbiological sensitivity testing that the infection is caused by sensitive bacteria. Tenkasi must not be used for the treatment of ABSSSI unless it is considered inappropriate to use the antibacterial agents that are recommended for the initial treatment of these infections. Consideration should be given to official guidance on the appropriate use of antibacterial agents. It is recommended that the decision to prescribe Tenkasi and initiation of therapy occur in a hospital setting under the direction of a specialist, e.g. specialist in infectious diseases.

2.2.2 Approved indication

Tenkasi is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and **paediatric patients aged 3 months and older** (see "Dosage/Administration", "Warnings and precautions" and "Properties/Effects") if it is established or strongly suspected after microbiological sensitivity testing that the infection is caused by sensitive bacteria. Tenkasi must not be used for the treatment of ABSSSI unless it is considered inappropriate to use the antibacterial agents that are recommended for the initial treatment of these infections. Consideration should be given to official guidance on the appropriate use of antibacterial agents. It is recommended that the decision to prescribe Tenkasi and initiation of therapy occur in a hospital setting under the direction of a specialist, e.g. specialist in infectious diseases.

2.2.3 Requested dosage

Summary of the requested standard dosage for the extension of indication:
Children and adolescents aged 3 months to under 18 years.
15 mg/kg administered as a single dose by intravenous infusion over 3 hours (maximum 1,200 mg).
Please refer to Table 1 for relevant example, and to "Other information" for further details.

Table 1: Oritavancin dose of 15 mg/kg body weight: 3-hour infusion (concentration of 1.2 mg/mL)

Patient's weight (kg)	Calculated oritavancin dose (mg)	Total infusion volume (mL)	Volume of reconstituted oritavancin (mL)	Volume of D5W to add to IV bag (mL)
5	75	62.5	7.5	55
10	150	125	15	110
15	225	187.5	22.5	165
20	300	250	30	220
25	375	312.5	37.5	275
30	450	375	45	330
35	525	437.5	52.5	385
40	600	500	60	440

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	11 April 2023
Formal control completed	3 May 2023
Preliminary decision	28 August 2023
Response to preliminary decision	28 September 2023
Final decision	15 November 2023
Decision	approval

3 Medical context

Acute bacterial skin and skin structure infections (ABSSSI) are inflammatory microbial invasions of the epidermis, dermis, and subcutaneous tissues. These infections include cellulitis, major cutaneous abscesses, and wound infections.

In some cases, ABSSSI can be serious and potentially life-threatening. The clinical complications of improperly treated or untreated ABSSSI include local expansion and spread, secondary bacteraemia with potential for distant metastatic foci of infection, and systemic effects of bacterial infection. ABSSSI are frequently caused by Gram-positive bacteria, including methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *Streptococcus pyogenes*, and other streptococcal species.

Treatment approaches for ABSSSI are dependent on the clinical presentation and the severity of infection, and include surgical drainage or debridement (as appropriate) and appropriate antibiotic therapy covering the implicated pathogen(s). The majority of these are usually susceptible to well-established antibiotics classes (e.g. beta-lactams), but some such as MRSA require the use of other treatment options such as vancomycin, daptomycin, and linezolid. Oritavancin is a semi-synthetic lipoglycopeptide with a long terminal half-life, active against Gram-positive bacteria including MRSA

4 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable since there are no changes with regard to posology and method of administration.
Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.
From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

5 Clinical and clinical pharmacology aspects

The evaluation of the pharmacokinetic/pharmacodynamic and clinical data of this application has been carried out in reliance on previous regulatory decisions by the EMA. The available EMA assessment report and the corresponding product information for Tenkasi (Assessment Report EMA/CHMP/783414/2023, dated 30 March 2023) were used as a basis for the pharmacokinetic / pharmacodynamic and clinical evaluation.

For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see Chapter 7.1 of this report.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Tenkasi was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Tenkasi 400 mg powder for concentrate for solution for infusion

Composition

Active substances

Oritavancinum ut Oritavancini diphosphas.

Excipients

Mannitol, phosphoric acid (for pH-adjustment).

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion (i.v.):
Each vial contains oritavancin diphosphate equivalent to 400 mg oritavancin.
After reconstitution, 1 ml of the solution contains 10 mg oritavancin. After dilution, 1 ml of the solution for infusion contains 1.2 mg oritavancin (see „other information“, handling instructions).
White to off-white powder.

Indications/Uses

Tenkasi is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and paediatric patients aged 3 months and older (see „Dosage/Administration”, „Warnings and precautions“ and „Properties/Effects“) if it is established or strongly suspected after microbiological sensitivity testing that the infection is caused by sensitive bacteria. Tenkasi must not be used for the treatment of ABSSSI unless it is considered inappropriate to use the antibacterial agents that are recommended for the initial treatment of these infections. Consideration should be given to official guidance on the appropriate use of antibacterial agents. It is recommended that the decision to prescribe Tenkasi and initiation of therapy occur in hospital setting under the direction of a specialist, e.g. specialist in infectious diseases.

Dosage/Administration

Usual dosage

Adults

1’200 mg administered as a single dose by intravenous infusion over 3 hours.
Another treatment with oritavancin should not be initiated within 50 days of the previous treatment.

Paediatric patients aged 3 months to < 18 years

15 mg/kg administered as a single dose by intravenous infusion over 3 hours (maximum 1 200 mg). Please refer to Table 1 for relevant example, and to section „other information“ for further details.

Table 1: 15 mg/kg Body Weight Dose of Oritavancin: 3-Hour Infusion (Concentration of 1.2 mg/ml)

Patient’s Weight (kg)	Calculated Oritavancin Dose (mg)	Total Infusion Volume (ml)	Volume of Reconstituted Oritavancin (ml)	Volume of D5W to add to IV Bag (ml)
5	75	62.5	7.5	55
10	150	125	15	110
15	225	187.5	22.5	165
20	300	250	30	220
25	375	312.5	37.5	275
30	450	375	45	330
35	525	437.5	52.5	385
40	600	500	60	440

A new treatment with oritavancin should not be initiated within 50 days of the previous treatment.

Special dosage instructions

Patients with impaired hepatic function

No dosage adjustment is required for patients with mild to moderate hepatic impairment (Child-Pugh Class B) (see „Pharmacokinetics“). The pharmacokinetics of oritavancin in patients with severe hepatic impairment (Child-Pugh Class C) has not been evaluated.

Patients with impaired renal function

No dosage adjustment is needed in patients with mild or moderate renal impairment (see „Pharmacokinetics“). The pharmacokinetics of oritavancin in patients with severe renal impairment has not been evaluated. Oritavancin is not removed from blood by haemodialysis procedures.

Elderly patients

No dosage adjustment is required for patients ≥ 65 years of age (see „Pharmacokinetics“).

Children and adolescents

The safety and efficacy of oritavancin in paediatric patients < 3 months of age have not yet been established.

Mode of administration

Intravenous use.
Intravenous infusion over 3 hours (see „other information“, handling instructions).
For instructions on reconstitution and dilution of the medicinal product before administration, see „other information“, handling instructions.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Compositions”.
Use of intravenous unfractionated heparin sodium is contraindicated for 120 hours (5 days) after oritavancin administration because the activated partial thromboplastin time (aPTT) test results may remain falsely elevated for up to 120 hours after oritavancin administration (see “Warning and Precautions” and “Interactions”).

Warnings and precautions

Hypersensitivity reactions
Serious hypersensitivity reactions, including anaphylactic reactions and anaphylactic shock have been reported with the use of oritavancin. If an acute hypersensitivity reaction occurs during oritavancin infusion, oritavancin should be discontinued immediately and appropriate supportive care should be instituted.
No data are available on cross-reactivity between oritavancin and other glycopeptides, including vancomycin. Before using oritavancin it is important to inquire carefully about previous hypersensitivity reactions to glycopeptides (e.g. vancomycin, telavancin (not marketed in Switzerland)). Due to the possibility of cross-hypersensitivity, there should be careful monitoring of patients with any history of glycopeptide hypersensitivity during and after the infusion.
Infusion related reactions
Oritavancin is given via intravenous infusion over 3 hours to minimise the risk of infusion related reactions. Intravenous infusions of oritavancin can cause reactions such as flushing of the upper body, urticaria, pruritis and/or rash. Infusion-associated reactions characterised by chest pain, chest discomfort, chills, tremor, back pain, neck pain, dyspnoea, hypoxia, abdominal pain and fever have been observed with the use of oritavancin, including after the administration of more than one dose of

oritavancin during a single course of therapy If reactions do occur, stopping or slowing the infusion may result in cessation of these symptoms (see „Undesirable effects“).

Need for additional antibacterial agents

Oritavancin is active against Gram positive bacteria only (see „Properties/Effects“). In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, oritavancin should be co-administered with appropriate antibacterial agent(s).

Concomitant use of oral anticoagulants and low molecular weight heparin (LMWH)

Oritavancin has been shown to interfere with certain laboratory coagulation tests (see *Interference with assay for coagulation tests and Interactions*). This should be considered for patients receiving oral anticoagulants requiring monitoring (vitamin K antagonists such as warfarin, phenprocoumon, acenocoumarol) as the prothrombin time (PT) and international normalised ratio (INR) may be artificially prolonged by oritavancin for up to 12 hours, making the monitoring of the anticoagulation effect unreliable during this period. In case of need, the anticoagulation effect of vitamin K antagonists, direct oral anticoagulant drugs (dabigatran, rivaroxaban, apixaban, edoxaban) and LMWH (e.g. dalteparin, enoxaparin, nadroparin) may be controlled with the chromogenic Factor Xa assay or the Thrombin Time (TT) assay as these are not affected by oritavancin. In cases where fondaparinux is required and levels can be obtained in a timely fashion, the chromogenic Factor Xa assay can be used approximately three hours after the dose is administered. The chromogenic Factor Xa activity assay must be calibrated using fondaparinux as a reference standard..

Interference with assay for coagulation tests

Oritavancin has been shown to interfere with certain laboratory coagulation tests (see “Contraindications” and “Interactions”). Oritavancin concentrations that are found in the blood of patients following administration of a single dose have been shown to artificially prolong:

- aPTT for up to 120 hours,
- PT and INR for up to 12 hours,
- Activated Clotting Time (ACT) for up to 24 hours,
- Silica Clot Time (SCT: Clotting test using silicon as an activator) for up to 18 hours, and
- Dilute Russell’s Viper Venom Test (DRVVT: Test using the venom of the chain viper as activator) for up to 72 hours.

These effects result from oritavancin binding to and preventing the action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests.

For patients who require aPTT monitoring within 120 hours of oritavancin dosing, a non-phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT monitoring may be considered.

The chromogenic Factor Xa assay, the TT assay and the assays used for the diagnosis of Heparin Induced Thrombocytopenia (HIT) are not affected by oritavancin. *In vitro*, oritavancin 46.6 µg/mL did not affect an assay for activated protein C resistance (APCR), suggesting that there is a low likelihood

that oritavancin will interfere with this test. However, APCR is a phospholipid-based test and it cannot be ruled out that higher concentrations of oritavancin that may occur during clinical use could interfere with this test.
No effect of oritavancin on the *in vivo* coagulation system was observed in nonclinical and clinical studies.
Clostridioides difficile-associated diarrhoea
Antibacterial-associated colitis and pseudomembranous colitis have been reported for oritavancin and may range in severity from mild to life threatening diarrhoea. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of oritavancin (see „Undesirable effects“). In such a circumstance, the use of supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered.
Superinfection
The use of antibacterial medicinal products may increase the risk of overgrowth of non-susceptible micro-organisms. If superinfection occurs, appropriate measures should be taken.
Osteomyelitis
In Phase 3 ABSSSI clinical trials, more cases of osteomyelitis were reported in the oritavancin-treated arm than in the vancomycin-treated arm (see „Undesirable effects“). Patients should be monitored for signs and symptoms of osteomyelitis after administration of oritavancin. If osteomyelitis is suspected or diagnosed, appropriate alternative antibacterial therapy should be instituted.
Abscess
In the Phase 3 clinical trials, slightly more cases of newly emergent abscesses were reported in the oritavancin-treated arm than in the vancomycin-treated arm (4.6% vs 3.4%, respectively) (see „Undesirable effects“). If newly emergent abscesses occur, appropriate measures should be taken.
Macrophage accumulation
In in vitro studies, Tenkasi accumulates within macrophages in a time- and concentration-dependent manner (see preclinical data). The clinical relevance of this accumulation is currently unknown.
Limitations of the clinical data
In the two major trials in ABSSSI the types of infections treated were confined to cellulitis, abscesses and wound infections only. Other types of infections have not been studied. There is limited experience in clinical studies in patients with bacteraemia, peripheral vascular disease or neutropenia, in immunocompromised patients, in patients aged > 65 years and in infections due to *S. pyogenes*.

Interactions¨

Drug transporter
The potential for oritavancin to interact with transporters has not been characterized. Caution should be exercised when concomitantly administering transporter substrates with narrow therapeutic windows.

Substances metabolised by cytochrome P450

A screening drug-drug interaction study was conducted in healthy volunteers (n=16) evaluating the concomitant administration of a single 1’200 mg dose of oritavancin with probe substrates for several CYP450 enzymes. Oritavancin was found to be a nonspecific, weak inhibitor (CYP2C9 and CYP2C19) or a weak inducer (CYP3A4 and CYP2D6) of several CYP isoforms.

Caution should be used when administering oritavancin concomitantly with medicinal products with a narrow therapeutic window that are predominantly metabolised by one of the affected CYP450 enzymes (e.g., warfarin), as co-administration may increase (e.g., for CYP2C9 substrates) or decrease (e.g., for CYP2D6 substrates) concentrations of the narrow therapeutic range medicinal product. Patients should be closely monitored for signs of toxicity or lack of efficacy if they have been given oritavancin while on a potentially affected compound (e.g. patients should be monitored for bleeding, if concomitantly receiving oritavancin and warfarin) (see “Warnings and precautions”). A study to assess the drug-drug interaction effect of a single 1’200mg dose of oritavancin on the pharmacokinetics of S-warfarin following a single dose was conducted in 36 healthy subjects. S-warfarin pharmacokinetics were evaluated following a single dose of warfarin 25 mg given alone, or administered at the start, 24, or 72 hours after a single 1’200 mg dose of oritavancin. The results showed no effect of oritavancin on S-warfarin AUC and C_{max}.

Other interactions

Drug-laboratory test interactions (see “Contraindications” and “Warnings and precautions”)

Coagulation tests

Oritavancin binds to and prevents the action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests. Oritavancin concentrations achieved in the blood after 1’200 mg doses may produce falsely elevated results from certain laboratory tests (see Table 2).

Table 2: Coagulation tests affected by oritavancin

Assay	**Duration of interference**
Prothrombin time (PT)	Up to 12 hours
International normalized ratio (INR)	Up to 12 hours
Activated partial thromboplastin time (aPTT)	Up to 120 hours
Activated clotting time (ACT)	Up to 24 hours
Silica clot time (SCT)	Up to 18 hours
Dilute Russell’s viper venom time (DRVVT)	Up to 72 hours

For patients who require monitoring of anticoagulation effect within the indicated times after oritavancin dosing, a non-phospholipid dependent coagulation test such as a Factor Xa (chromogenic) or TT should be considered.

Positive Indirect and Direct Antiglobulin Tests (IAT/DAT)
Positive IAT/DAT were noted with administration of oritavancin products, including Tenkasi, in studies with healthy volunteers and patients with ABSSSI. Positive IAT may interfere with cross-matching before blood transfusion.

Pregnancy, lactation

Pregnancy

There are no or limited amount of data from the use of oritavancin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see *"preclinical data"*). As a precautionary measure**,** oritavancin should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Lactation

Available pharmacodynamic/toxicological data in animals have shown excretion of oritavancin in milk (see „Preclinical data"). It is unknown whether oritavancin is excreted in human milk. A risk to the newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from oritavancin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies have revealed no evidence of impaired fertility due to oritavancin at the highest concentrations administered, however, there is no data on the effects of oritavancin on human fertility.

Effects on ability to drive and use machines

Oritavancin has a minor influence on the ability to drive and use machines. Dizziness may occur and this may have an effect on driving and use of machines (see „Undesirable effects").

Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions (≥5%) were: nausea, hypersensitivity reactions, infusion site reactions, and headache. The most commonly reported serious adverse reaction was cellulitis (1.1%). The most common reported reasons for discontinuation were cellulitis (0.4%) and osteomyelitis (0.3%). Female patients had a higher reporting rate for adverse reactions than male patients.

Listing of adverse reactions
Adverse reactions for oritavancin from the pooled Phase 3 ABSSSI clinical trials with single dose oritavancin are listed by system organ class.
Frequencies are defined as: 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); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations
Common: Cellulitis, abscess (limb and subcutaneous).
Uncommon: Osteomyelitis.

Blood and lymphatic system disorders
Common: Anaemia.
Uncommon: Eosinophilia, thrombocytopenia.

Immune system disorders
Uncommon: Hypersensitivity (see „Contraindications“ und „Warnings and precautions“), anaphylactic reaction.
Unknown: Anaphylactic shock.

Metabolism and nutrition disorders
Uncommon: Hypoglycaemia, hyperuricaemia.

Nervous system disorders
Common: Headache, dizziness.
Rare: Tremor*.

Cardiac disorders
Common: Tachycardia.

Respiratory, thoracic and mediastinal disorders
Uncommon: Bronchospasm, wheezing, dyspnoea*.
Rare: Hypoxia*.

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhoea, constipation.
Uncommon: Abdominal pain*.

Hepatobiliary disorders
Common: Liver function test abnormal (Alanine aminotransferase increased, Aspartate aminotransferase increased).
Uncommon: Blood bilirubin increased.

Skin and subcutaneous tissue disorders
Common: Urticaria, rash, pruritis.
Uncommon: Leucocytoclastic vasculitis, angioedema, erythema multiforme, flushing.

Musculoskeletal and connective tissue disorders
Common: Myalgia.
Uncommon: Tenosynovitis.
Rare: Back pain*, neck pain*.

General disorders and administration site conditions
Common: Infusion site reactions, including the following symptoms infusion site phlebitis, infusion site erythema, extravasation, induration, pruritis, rash, oedema peripheral.
Uncommon: Chest pain*, pyrexia*.
Rare: Flushing reactions, chest discomfort*, chills*

**These reactions may be infusion-related (see section Warnings and precautions)*

Paediatric population
The safety assessment in paediatric patients is based on data from one trial in which 38 patients aged from 3 months to 18 years with suspected or confirmed Gram-positive bacterial infection received Tenkasi. Overall, the safety profile in these 38 patients was similar to that observed in the adult population. The following ADRs not reported for adult patients have been observed in no more than 1 paediatric patient: irritability, electrocardiogram QT prolonged (transient, asymptomatic and not associated to other ECG abnormalities), *Clostridioides difficile* colitis (see section “Warnings and precautions”).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In the clinical programme of 3'017 oritavancin-treated subjects, there was no incidence of accidental overdose of oritavancin.

Treatment

Oritavancin is not removed from blood by haemodialysis procedures. In the event of overdose, supportive measures should be taken.

Properties/Effects

ATC code

J01XA05

Mechanism of action

Oritavancin has three mechanisms of action: (i) inhibition of the transglycosylation (polymerisation) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors; (ii) inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall; and (iii) disruption of bacterial membrane integrity, leading to depolarisation, permeabilisation, and rapid cell death.

Resistance

Gram-negative organisms are intrinsically resistant to all glycopeptides, including oritavancin. Resistance to oritavancin was observed *in vitro* in vancomycin-resistant isolates of *Staphylococcus aureus*. There is no known cross-resistance between oritavancin and non-glycopeptide classes of antibiotics.
Oritavancin exhibits reduced *in vitro* activity against certain Gram-positive organisms of the genera *Lactobacillus*, *Leuconostoc* and *Pediococcus* that are intrinsically resistant to glycopeptides.

Susceptibility testing break points

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Table 3: Susceptibility Interpretive Criteria for Oritavancin

Organism group	**MIC breakpoints (mg/L)**

	S ≤	**R >**
Staphylococcus aureus	0.125	0.125
Beta-haemolytic streptococci Groups A, B, C, G	0.25	0.25
Viridans group streptococci (*S. anginosus* group only)	0.25	0.25

S=Susceptible, R=Resistant

Pharmacodynamics

The area under the concentration-time curve (AUC) to minimum inhibitory concentration (MIC) ratio of oritavancin for the infecting organism has been shown to be the parameter that best correlates with efficacy.

Clinical efficacy

Efficacy has been demonstrated in clinical studies against the following pathogens that were susceptible to oritavancin *in vitro*.

Gram-positive microorganisms:

- *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 oritavancin in the absence of acquired mechanisms of resistance:

- Beta-haemolytic streptococci of Group G
- *Clostridium perfringens*
- *Peptostreptococcus* spp.

The efficacy of Tenkasi has been established in two identical randomized clinical trials (Trial 1 and Trial 2) performed in patients with acute bacterial skin and skin structure infections (ABSSSI) comparing a single 1200 mg intravenous dose of Tenkasi to intravenous vancomycin (1 g or 15 mg/kg every 12 hours) for 7 to 10 days. Patients could receive concomitant aztreonam or metronidazole for suspected Gram-negative and anaerobic infection, respectively.

The primary analysis population (modified intent to treat, mITT) included all randomized patients who received any study drug.

The primary endpoint (in Europe) for both trials was the rate of investigator-assessed clinical cure at Post Therapy Evaluation (PTE) (i.e., 7 to 14 days after the end of study therapy). This endpoint was prespecified for non-inferiority testing with a margin of 10%.

The key secondary efficacy endpoint (primary in US) was early clinical response, a composite endpoint defined as the cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication at Early Clinical Evaluation (ECE) (i.e., 48 to 72 hours from initiation of first study drug infusion). This endpoint was prespecified for non-inferiority testing with a margin of 10%.

Trial 1

Of the 968 patients randomized, a total of 954 patients (475 in the oritavancin group and 479 in the vancomycin group) received at least one dose of study drug, and thus, were included in the mITT population.

The oritavancin and vancomycin groups were similar with respect to demographic and baseline disease characteristics. Most patients in both groups were male (oritavancin, 63.4%; vancomycin, 62.8%), and White (oritavancin, 57.7%; vancomycin, 57.4%). Mean age was 46.2 years (range: 18-89 years) in the oritavancin group and 44.3 years (range: 18-93 years) in the vancomycin group. Patients in the study were primarily enrolled in North America (62.7%) and Asia (31.0%). The types of ABSSSI included cellulitis/erysipelas (49.9%), major cutaneous abscesses (29.5%), and wound infection (20.6%). The majority of wound infections were related to trauma (81.5% and 83.8% for oritavancin and vancomycin patients, respectively). The median infection area at baseline was 248.0 cm^2 for the oritavancin group and 225.6 cm^2 for the vancomycin group.

Trial 1 Efficacy Results (mITT Population)

	Oritavancin % (n/N)	**Vancomycin % (n/N)**	**Difference (two-sided 95% CI)**
Investigator-assessed clinical cure at PTE	79.6% (378/475)	80.0% (383/479)	-0.4 (-5.5, 4.7)
Early clinical response	82.3% (391/475)	78.9% (378/479)	3.4 (-1.6, 8.4)

CI: confidence intervals;; PTE: Post Therapy Evaluation;

Trial 2

Of the 1019 patients randomized, a total of 1005 patients (503 in the oritavancin group and 502 in the vancomycin group) received at least one dose of study drug, and thus, were included in the mITT population.

The oritavancin and vancomycin groups in trial 2 were similar with respect to demographic and baseline disease characteristics. Most patients in both groups were male (oritavancin, 67.2%; vancomycin, 68.3%), and White (oritavancin, 70.8%; vancomycin, 70.9%). Mean age was 45.0 years (range: 18-85 years) in the oritavancin group and 44.4 years (range: 18-92 years) in the vancomycin group. Patients in the study were primarily enrolled in North America (56.9%) and Asia (23.6%). There was no difference in baseline disease characteristics and characteristics of the primary infection site between the groups. Infection types were balanced in the oritavancin and vancomycin groups. The types of ABSSSI included wound infection (36.5%) major cutaneous abscesses (32.5%), and cellulitis/erysipelas (30.9%).The majority of wound infections were related to trauma (83.8% and 81.3% for oritavancin and vancomycin patients, respectively). The median infection area at baseline was 287.8 cm^2 for the oritavancin group and 308.8 cm^2 for the vancomycin group.

Trial 2 Efficacy Results (mITT Population)

	Oritavancin % (n/N)	**Vancomycin % (n/N)**	**Difference (two-sided 95% CI)**
Investigator-assessed clinical cure at PTE	82.7% (416/503)	80.5% (404/502)	2.2 (-2.6, 7.0)
Early clinical response	80.1% (403/503)	82.9% (416/502)	-2.7 (-7.5, 2.0)

CI: confidence intervals;; PTE: Post Therapy Evaluation

Outcomes by Baseline Pathogen (MicroITT Population) pooled analysis of Trial 1 and Trial 2

	Investigator-Assessed Clinical Cure Rate at PTE			**Early Clinical Response Rate at ECE**		
	Oritavancin N=529 % (n/N)	**Vancomycin N=538 % (n/N)**		**Oritavancin N=529 % (n/N)**	**Vancomycin N=538 % (n/N)**	
S. aureus	389/470 (82.8)	393/468 (84.0)		388/470 (82.6)	391/468 (83.5)	
MSSA	220/268 (82.1)	229/272 (84.2)		222/268 (82.8)	233/272 (85.7)	
MRSA	170/204 (83.3)	169/201 (84.1)		166/204 (81.4)	162/201 (80.6)	
S. lugdunensis	4/4 (100.0)	4/5 (80.0)		4/4 (100.0)	3/5 (60.0)	
S. pyogenes	25/31 (80.6)	23/32 (71.9)		21/31 (67.7)	23/32 (71.9)	
S. constellatus	15/19 (78.9)	19/23 (82.6)		17/19 (89.5)	21/23 (91.3)	
S. intermedius	8/10 (80.0)	13/16 (81.3)		8/10 (80.0)	13/16 (81.3)	
S. agalactiae	7/8 (87.5)	11/12 (91.7)		7/8 (87.5)	12/12 (100.0)	
S. dysgalactiae	7/9 (77.8)	3/6 (50.0)		7/9 (77.8)	6/6 (100.0)	
S. anginosus	2/4 (50.0)	6/6 (100.0)		3/4 (75.0)	6/6 (100.0)	
E. faecalis	8/13 (61.5)	9/12 (75.0)		11/13 (84.6)	10/12 (83.3)	
E. faecium	0/0	0/1		0/0	1/1 (100.0)	

ECE: Early Clinical Evaluation; MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-susceptible *S. aureus*; NE: Not Evaluable; PTE: Post Therapy Evaluation;

Cardiac Electrophysiology

In a thorough QTc study of 135 healthy subjects at a dose 1.3 times the 1200 mg recommended dose, Orbactiv did not prolong the QTc interval to any clinically relevant extent.

Safety and efficacy in paediatric patients

Tenkasi has been evaluated in paediatric patients with ABSSSI in one Phase 1 open-label, multicentre trial that included 38 patients aged from 3 months to < 18 years who have been dosed with oritavancin. Its objective was to evaluate the PK, safety, and tolerability of an intravenous (IV) infusion of oritavancin in patients with a suspected or confirmed Gram-positive bacterial infection who received standard antibiotic therapy or in patients receiving peri-operative antibiotic prophylaxis. The primary endpoint was the area under the plasma concentration-time curve (AUC); secondary endpoints include safety evaluation and other PK parameters.

Swissmedic has deferred the obligation to submit the results of studies with oritavancin in paediatric population aged 0 to <3 months in the treatment of acute bacterial skin and skin structure infections (see “Dosage/Administartion” for information on paediatric use).

Pharmacokinetics

The mean (CV%) maximum oritavancin concentration (C_{max}) and $AUC_{0-\infty}$ in patients receiving a single 1’200 mg dose in ABSSSI patients is 138 (23) µg/ml and 2’800 (28.6) µg•h/mL respectively. The mean oritavancin concentration-time profile displays a multi-exponential decline with a long terminal plasma half-life.

Absorption

Not applicable.

Distribution

Oritavancin is approximately 85% bound to human plasma proteins. Based on population PK analysis, the population mean total volume of distribution is estimated to be approximately 87.6 L, indicating oritavancin is extensively distributed into the tissues.
Exposures (AUC_{0-24}) of oritavancin in skin blister fluid were 20% of those in plasma after a single 800 mg dose in healthy subjects.

Metabolism

No metabolites were observed in plasma or bile from oritavancin treated dogs and rats, respectively. Additionally, *in vitro* human liver microsome studies indicated that oritavancin is not metabolised.

Elimination

No mass balance study has been conducted in humans. In humans, less than 1% to 5% of the dose was recovered as parent drug in faeces and urine respectively after 2 weeks of collection.
The mean terminal elimination plasma half-life of oritavancin is 245 hours (14.9% CV) based on population PK analysis of ABSSSI patients receiving a single 1’200 mg dose. The population mean total clearance is estimated at 0.445 L/h (27.2 % CV).
Linearity/non-linearity

Oritavancin exhibits linear pharmacokinetics at a dose up to 1’200 mg.
Kinetics in specific patient groups

Hepatic impairment

The pharmacokinetics of oritavancin were evaluated in a study of subjects with moderate hepatic impairment (Child-Pugh Class B, n=20) and compared with healthy subjects (n=20) matched for gender, age and weight. There were no relevant changes in pharmacokinetics of oritavancin in patients with moderate hepatic impairment.
The pharmacokinetics of oritavancin in patients with severe hepatic impairment has not been studied.

Renal impairment

The pharmacokinetics of oritavancin was examined in the single dose Phase 3 ABSSSI studies in patients with normal renal function, CrCL ≥90 mL/min (n=213), mild renal impairment, CrCL 60-89 mL/min (n=59), moderate renal impairment, CrCL 30-59 mL/min (n=22), and severe renal impairment CrCL <30 mL/min (n=3). Population pharmacokinetic analysis indicated that renal impairment had no clinically relevant effect on the exposure of oritavancin. No dedicated studies in dialysis patients have been conducted. The pharmacokinetics of oritavancin in patients with severe renal impairment has not been evaluated.

Effects of age, weight, gender and race

Population PK analysis from the single dose Phase 3 ABSSSI studies in patients indicated that gender, age, weight, or race had no clinically relevant effect on the exposure of oritavancin. No dosage adjustment is warranted in these subpopulations.

Paediatric population

Compartmental population PK analysis showed that a dose of 15 mg/kg produced a mean model-derived AUC_{0-72} that fell within the adult target range (965 - 2095 µg•h/mL) for all simulated paediatric groups ranging from 3 months to <18 years (please refer to Table 4).

Table 4: Model-derived oritavancin pharmacokinetic parameters [mean (SD)] for paediatrics and adults using population PK analysis

Population	***AUC_{0-72} (µg•h/mL)*** *Mean (SD)*	***C_{max} (µg/mL)*** *Mean (SD)*
Adults	1530 (565)	138 (31.7)
12 to <18 years	2065.5 (408.23)	117.0 (25.09)
6 to <12 years	1766.9 (362.66)	107.4 (22.73)
2 to < 6 years	1556.6 (319.32)	102.5 (21.11)
From 3 months to <2 years	1456.6 (309.24)	103.0 (21.19)

Preclinical data

Long-term toxicity (or repeat dose toxicity)

The primary adverse effect of oritavancin administration to rats and dogs was a dose related accumulation of eosinophilic granules in tissue macrophages including hepatocytes, renal cortical epithelial cells, adrenal cells and macrophages of the reticulo endothelial system. The appearance of the eosinophilic granules did not occur following single dose administration and did not significantly affect innate macrophage function *in vitro* at intracellular levels anticipated from a single 1’200 mg dose.

Moderate, dose-related increases in liver enzymes (alanine transaminase and aspartate transaminase) were observed in rats and dogs and were shown to be reversible upon cessation of treatment. Biochemistry changes associated with kidney function including decreases in urine-specific gravity and pH and slight increases in blood urea nitrogen and sporadic increases in creatinine were present in both rat and dog after treatment of two weeks. Extramedullary haematopoiesis in the spleen was observed in rats. This histopathological finding correlated with an enlargement and an increase in the weight of the spleen. The exposure in rats at the no observed adverse effect level (NOAEL) was less to only slightly higher than the human exposure based on the AUC.

Histamine-like infusion reactions following immediately or shortly after dosing with oritavancin occurred in both rats and dogs. These reactions were associated with mortality at lower dosages in male than in female rats in single dose studies; however, the same gender-related differences were not observed in other species. Studies in neonatal rats and dogs for 30 days showed the same tissue effects as those seen in adult animals including sensitivity to the oritavancin-mediated histamine-like infusion reactions. Mortality was observed in neonatal rats at slightly lower dosage levels than in adults.

Mutagenicity/Carcinogenicity

A standard battery of *in vitro* and *in vivo* tests on the genotoxic potential did not reveal any clinically relevant findings. Lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of oritavancin.

Reproductive toxicity

When administered intravenously at doses up to 30 mg/kg, oritavancin did not affect the fertility or reproductive performance of male and female rats. Studies in pregnant rats and rabbits do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. There was no evidence of transplacental transfer of oritavancin in pregnant rats. The exposure in rats at the NOAEL was less to only slightly higher than the human exposure based on the AUC.

Following a single intravenous infusion in lactating rats, radio-labelled $^{[14C]}$oritavancin was excreted in milk and absorbed by nursing pups.

Other information

Incompatibilities

Sodium chloride solution should not be used for dilution as it is incompatible with oritavancin and may cause precipitation of the medicinal product. Therefore, other substances, additives or other medicinal products mixed in sodium chloride solution for intravenous use should not be added to oritavancin single-use vials or infused simultaneously through the same intravenous line or through a common intravenous port. In addition, medicinal products formulated at a basic or neutral pH may be incompatible with oritavancin (see „other information“, handling instructions).

Effects on diagnostic methods

Oritavancin binds to and prevents the action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests. Oritavancin concentrations achieved in the blood after 1’200 mg doses may produce falsely elevated results from certain laboratory tests (see “contraindications“, „warnings and precautions“ und „interactions“).

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

After reconstitution

The reconstituted solution should be further diluted in glucose 50 mg/ml (5%) intravenous infusion bag immediately.

After dilution

The diluted solution should be used immediately.

From a microbiological point of view, the product should be used immediately. If not used immediately storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 25°C and 24 hours at 2-8°C following dilution in a glucose 5% intravenous infusion bag, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Do not store above 25°C.
Keep out of the reach of children.

Instructions for handling

For single use only. Tenkasi should be prepared under aseptic techniques. Three reconstituted vials are required for administration of a single intravenous use of 1’200 mg.
The powder must be reconstituted with water for injections and the resulting concentrate must be diluted in a glucose 5% intravenous infusion bag prior to use. Both the reconstituted solution and the diluted solution for infusion must be clear, colourless to pale yellow solution. Parenteral medicinal products should be inspected visually for particulate matter after reconstitution.

Adults

Reconstitution:

- 40 mL of water for injections (WFI) should be added using a sterile syringe to reconstitute each vial to provide a 10 mg/mL solution per vial.
- To avoid excessive foaming, it is recommended that WFI should be added carefully, along the walls of the vials.
- Each vial should be swirled gently to avoid foaming and ensure that all of the powder is completely reconstituted in solution.

Dilution: Three reconstituted vials are needed for dilution for administration of a single 1’200 mg intravenous infusion. Only glucose 5% intravenous bag (D5W) should be used for dilution. Sodium chloride solution should not be used for dilution (see”other information”, incompatibilities).
Dilution:

- Withdraw and discard 120 mL from a 1’000 mL D5W intravenous bag.
- Withdraw 40 mL from each of the three reconstituted vials and add to D5W intravenous bag to bring the bag volume to 1,000 mL. This yields a concentration of 1.2 mg/mL of oritavancin. PP (Polypropylene) or PVC (Polyvinyl chloride) bags should be used for administration preparation.

Use in the paediatric population (aged 3 months to < 18 years)

Calculate the dose of oritavancin required based on patient's weight (one single infusion of 15 mg/kg administered intravenously over 3 hours).
Determine the number of oritavancin vials that are required for the patient (each vial contains oritavancin diphosphate equivalent to 400 mg oritavancin).

Reconstitution:

- 40 mL of water for injections (WFI) should be added using a sterile syringe to reconstitute each vial to provide a 10 mg/mL solution per vial.
- To avoid excessive foaming, it is recommended that WFI should be added carefully, along the walls of the vials.
- Each vial should be swirled gently to avoid foaming and ensure that all of the powder is completely reconstituted in solution.

Dilution: Only glucose 5% intravenous bag (D5W) should be used for dilution. Sodium chloride solution should not be used for dilution (see section „other information", incompatibilities).

Dilution:
Withdraw the necessary volume of oritavancin with a sterile syringe and add to the IV bag containing sterile D5W (please refer to table 5 for relevant example). The size of the IV bag will be based on the total volume administered. For small volumes a syringe pump may be used.

Table 5: 15 mg/kg Oritavancin: 3-Hour Infusion (Concentration of 1.2 mg/ml)

Patient's Weight (kg)	Calculated Oritavancin Dose (mg)	Total Infusion Volume (ml)	Volume of Reconstituted Oritavancin (ml)	Volume of D5W to add to IV Bag (ml)
5	75	62.5	7.5	55
10	150	125	15	110
15	225	187.5	22.5	165
20	300	250	30	220
25	375	312.5	37.5	275
30	450	375	45	330
35	525	437.5	52.5	385
40	600	500	60	440

Calculations
1) Use Patient's Actual Weight—ROUND ONLY TO THE NEAREST WHOLE NUMBER

2) Dose: Weight (kg) x 15 mg/kg = _____ mg (Maximum Dose 1200 mg)

3) Total Infusion Volume: Dose (mg) ÷1.2 mg/ml = _____ ml

4) Volume of Reconstituted Oritavancin: Dose (mg) ÷ 10 =_____ ml

5) Volume of D5W to add to IV bag: Total Infusion Volume – Volume of Reconstituted Oritavancin = _____ ml

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

Authorisation number

68135 (Swissmedic).

Packs

Powder for solution for infusion: 3 vials [A].

Marketing authorisation holder

A. Menarini GmbH, Zürich.

Date of revision of the text

August 2023