SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tenkasi 400 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 sections 4.2, 4.4 and 5.1).

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

4.2 Posology and method of administration

Posology

Adults
1 200 mg administered as a single dose by intravenous infusion over 3 hours.

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 6.6 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

Special populations

Elderly (≥ 65 years)
No dose adjustment is required for patients ≥ 65 years of age (see section 5.2).

Renal impairment
No dose adjustment is needed in patients with mild or moderate renal impairment . Very limited data are available in patients with severe renal impairment. Renal impairment had no clinically relevant effect on the exposure of oritavancin (see section 5.2), however caution should be exercised when prescribing oritavancin in patients with severe renal impairment. Oritavancin is not removed from blood by haemodialysis procedures.

Hepatic impairment
No dose adjustment is required for patients with mild to moderate hepatic impairment (Child-Pugh Class B) (see section 5.2). The pharmacokinetics of oritavancin in patients with severe hepatic impairment (Child-Pugh Class C) has not been evaluated, however based on pharmacokinetic parameters, severe hepatic impairment is not expected to have an impact on oritavancin exposure. Therefore no dose adjustment is required, even if caution should be exercised when prescribing oritavancin to patients with severe hepatic impairment (Child-Pugh Class C).

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

Method of administration

Intravenous use.

There are two oritavancin medicinal products (Tenkasi 400 mg and Tenkasi 1 200 mg) that:
- Are supplied in different dose strengths of oritavancin.
- Have different recommended duration of infusion.
- Have different preparation instructions, including differences in reconstitution, dilution, and compatible diluents.

Carefully follow the recommended posology (see section 4.2) and the instructions on reconstitution and dilution for Tenkasi 400 mg before administration (see section 6.6).

Each of the three 400 mg vials should first be reconstituted with 40 mL of sterile water for injection (WFI). The reconstituted solutions should be withdrawn and added to a 1 000 mL glucose 5% intravenous bag (D5W) for an intravenous infusion over 3 hours (see section 6.6).

Only D5W should be used for dilution. Sodium chloride solution should not be used for dilution (see section 6.2)

Refer to Tenkasi 1 200 mg for relevant information on the other oritavancin medicinal product.

4.3 Contraindications

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

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 sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

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). 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, pruritus 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 section 4.8).

Need for additional antibacterial agents

Oritavancin is active against Gram-positive bacteria only (see section 5.1). 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 warfarin

Oritavancin has been shown to artificially prolong prothrombin time (PT) and international normalised ratio (INR) for up to 12 hours, making the monitoring of the anticoagulation effect of warfarin unreliable up to 12 hours after an oritavancin dose.

Interference with assay for coagulation tests

Oritavancin has been shown to interfere with certain laboratory coagulation tests (see sections 4.3 and 4.5). 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) for up to 18 hours, and
- Dilute Russell's Viper Venom Test (DRVVT) 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 Thrombin Time (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 section 4.8). 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 section 4.8). 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 section 4.8). If newly emergent abscesses occur, appropriate measures should be taken.

Limitations of the clinical data

In the two major trials in ABSSSI, the types of infections treated were confined to cellulitis, abscesses, and wound infection 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, in patients with severe renal impairment and in infections due to *Streptococcus pyogenes*.

4.5 Interaction with other medicinal products and other forms of interaction

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 section 4.4). A study to assess the drug-drug interaction effect of a single 1 200 mg 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}.

Drug-laboratory test interactions (see sections 4.3 and 4.4)

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of oritavancin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure**,** it is preferable to avoid the use of Tenkasi during pregnancy unless the clinical condition of the woman requires treatment with oritavancin.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of oritavancin in milk (for details see section 5.3). It is unknown whether oritavancin/metabolites are 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 Tenkasi 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 are no data on the effects of oritavancin on human fertility.

4.7 Effects on ability to drive and use machines

Tenkasi 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 section 4.8).

4.8 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.

Tabulated list 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 in the following table.

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 <1/1000); very rare (<1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3:Frequency of adverse reactions by system organ class

System organ class	Frequency	Adverse Reactions
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 sections 4.3 and 4.4), 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, pruritus
	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**

	Uncommon	Chest pain*, pyrexia*
	Rare	Chest discomfort*, chills*

*These reactions may be infusion-related (see section 4.4)
** Infusion site reactions includes: infusion site phlebitis, infusion site erythema, extravasation, induration, pruritus, rash, oedema peripheral.

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 in Table 3 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 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the clinical programme of 3017 oritavancin-treated subjects, there was no incidence of accidental overdose of oritavancin.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, glycopeptide antibacterials, 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 4:Susceptibility Interpretive Criteria for Oritavancin

Organism group	**MIC breakpoints (mg/L)**	
	S ≤	**R >**
Staphylococcus aureus	0.125	0.125
*Streptococcus(*Groups A, B, C, G)	0.25	0.25
Viridans group streptococci (*S. anginosus* group only)	0.25	0.25

S=Susceptible, R=Resistant

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship

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 against specific pathogens

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.

Paediatric population

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Tenkasi in paediatric population aged 0 to <3 months in the treatment of acute bacterial skin and skin structure infections (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Oritavancin exhibits linear pharmacokinetics at a dose up to 1200 mg. The mean (±SD) maximum oritavancin concentration (C_{max}) and AUC_{0-72} in ABSSSI patients receiving a single 1 200 mg dose is 112 (±34.523) μg/ml and 1470 (±582) μg•h/mL respectively.

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.

Biotransformation

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 active substance in faeces and urine respectively after 2 weeks of collection indicating that oritavancin is slowly excreted unchanged.

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 1200 mg dose. The population mean total clearance is estimated at 0.445 L/h (27.2 % CV).

In a population PK analysis, a relationship between height and clearance was identified, where clearance increased with increasing height. Dose modification based on height is not necessary.

Special populations

Renal impairment
The pharmacokinetics of oritavancin were 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.
Dose adjustment of oritavancin is not needed in patients with mild or moderate renal impairment, wheras data on severe renal impairment are too limited to make dose adjustment recommendation.
.

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 subjects with moderate hepatic impairment.

Dose adjustment of oritavancin is not needed in patients with mild and moderate hepatic impairment. The pharmacokinetics of oritavancin in patients with severe hepatic impairment have not been studied.

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 dose 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 5).

Table 5: 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)

5.3 Preclinical safety data

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 reticuloendothelial 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 doses 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.

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Phosphoric acid (for pH-adjustment)

6.2 Incompatibilities

Sodium chloride solution should not be used for dilution, as it is incompatible with oritavancin 400 mg dosage strength 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 section 6.6).

6.3 Shelf life

4 years

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 °C -8 °C following dilution in a glucose 5% intravenous infusion bag.

6.4 Special precautions for storage

Do not store above 25 °C.

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

6.5 Nature and contents of container

Single-use 50 ml Type 1 glass vials with rubber stoppers and aluminium flip off cap.

3 individual vials are packaged in a carton.

6.6 Special precautions for disposal

For single use only. Tenkasi should be prepared under aseptic techniques

There are two oritavancin medicinal products (Tenkasi 400 mg and Tenkasi 1 200 mg) that:

- Are supplied in different dose strengths of oritavancin.
- Have different recommended duration of infusion.
- Have different preparation instructions, including differences in reconstitution, dilution, and compatible diluents.

Carefully follow the recommended instructions for each medicinal product.
Three Tenkasi 400 mg vials need to be reconstituted and diluted to prepare a single once-only 1 200 mg IV dose.

The powder must be reconstituted with sterile water for injection 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 should be clear, colourless to pale yellow solution. Parenteral medicinal products should be inspected visually for particulate matter after reconstitution.

<u>Adults</u>

Reconstitution:

- 40 mL of sterile water for injection (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 sterile 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 section 6.2).

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 1000 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 6.2).

Dilution:
Withdraw the necessary volume of oritavancin with a sterile syringe and add to the IV bag containing sterile D5W (please refer to table 6 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 6: 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 1 200 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 (C) – Volume of Reconstituted Oritavancin (D) = _____ ml

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

Refer to Tenkasi 1 200 mg for relevant information on the other oritavancin medicinal product.

7 MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare
L-1611, Luxembourg
Luxembourg

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 16239/0060

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

19/11/2024