

ANNEX I

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 (see sections 4.4 and 5.1).

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

4.2 Posology and method of administration

Posology

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

Special populations

Elderly (≥ 65 years)

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

Renal impairment

No dosage adjustment is needed in patients with mild or moderate renal impairment (see section 5.2). The pharmacokinetics of oritavancin in patients with severe renal impairment has not been evaluated. Oritavancin is not removed from blood by haemodialysis procedures.

Hepatic impairment

No dosage 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 children and adolescents (<18 years) have not yet been established. No data are available.

Method of administration

Intravenous use.

Intravenous infusion over 3 hours (see section 6.6).

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

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 that resemble “red man syndrome”, including flushing of the upper body, urticaria, pruritis and/or rash. Infusion-associated reactions characterized 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 (1200mg) 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 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*.

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 1,200mg 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 1,200mg 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 1).

Table 1: 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 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 oritavancin during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of oritavancin in milk (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 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.

4.7 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 section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions ($\geq 5\%$) 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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.

Table 2: 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, 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	Red man syndrome, chest discomfort*, chills*

*These reactions may be infusion-related (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 national reporting system** listed in [Appendix V](#).

4.9 Overdose

In the clinical programme of 3,017 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 (polymerization) 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 depolarization, permeabilization, 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 >
<i>Staphylococcus aureus</i>	0.125	0.125
<i>Beta-haemolytic streptococci</i> Groups A, B, C, G	0.25	0.25
Viridans group streptococci (<i>S. anginosus</i> 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

The European Medicines Agency has deferred the obligation to submit the results of studies with oritavancin in one or more subsets of the paediatric population 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 1,200 mg. 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.

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 metabolized.

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 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 1,200 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 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.

Dosage adjustment of oritavancin is not needed in patients with mild or moderate renal impairment. The pharmacokinetics of oritavancin in patients with severe renal impairment has not been evaluated.

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.

Dosage adjustment of oritavancin is not needed in patients with mild and moderate hepatic impairment. The pharmacokinetics of oritavancin in patients with severe hepatic impairment has 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 dosage adjustment is warranted in these subpopulations.

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 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.

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 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 2-8°C following dilution in a glucose 5% intravenous infusion bag, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

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 and other handling

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

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 should be clear, colourless to pale yellow solution. Parenteral medicinal products should be inspected visually for particulate matter after reconstitution.

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 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 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.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/989/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19/03/2015

Date of latest renewal: 13/01/2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Biologici Italia Laboratories S.r.l
Via Filippo Serpero 2
20060 Masate (MI)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Tenkasi 400 mg powder for concentrate for solution for infusion
oritavancin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains oritavancin diphosphate equivalent to 400 mg oritavancin.
After reconstitution and dilution, 1 ml solution for infusion contains 1.2 mg oritavancin.

3. LIST OF EXCIPIENTS

Mannitol
Phosphoric acid

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
3 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/989/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**VIAL LABEL****1. NAME OF THE MEDICINAL PRODUCT**

Tenkasi 400 mg powder for concentrate
oritavancin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Contains 400 mg oritavancin.

3. LIST OF EXCIPIENTS

Mannitol
Phosphoric acid

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/989/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tenkasi 400 mg powder for concentrate for solution for infusion oritavancin

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tenkasi is and what it is used for
2. What you need to know before you are given Tenkasi
3. How you will be given Tenkasi
4. Possible side effects
5. How to store Tenkasi
6. Contents of the pack and other information

1. What Tenkasi is and what it is used for

Tenkasi is an antibiotic that contains the active substance oritavancin. Oritavancin is a type of antibiotic (a lipoglycopeptide antibiotic) that can kill or stop the growth of certain bacteria.

Tenkasi is used to treat infections of the skin and underlying tissues.

It is for use in adults only.

Tenkasi can only be used to treat infections caused by bacteria known as Gram positive bacteria. In mixed infections where other types of bacteria are suspected, your doctor will give you other appropriate antibiotics together with Tenkasi.

2. What you need to know before you are given Tenkasi

You must not be given Tenkasi

- if you are allergic to oritavancin or any of the other ingredients of this medicine (listed in section 6).
- if it is expected that you may need to be given a blood thinning medicine (unfractionated heparin sodium) within 5 days (120 hours) of the dose of Tenkasi.

Warnings and precautions

Talk to your doctor or nurse before receiving Tenkasi if you:

- have ever had an allergic reaction to another glycopeptide antibiotic (such as vancomycin and telavancin)
- have developed severe diarrhoea during or following antibiotic treatment in the past.
- have or are suspected to have a bone infection caused by bacteria (osteomyelitis). Your doctor will treat you as necessary
- have or are suspected to have a painful collection of pus on your skin (abscess). Your doctor will treat you as necessary.

Intravenous infusions of Tenkasi can cause flushing of the upper body, hives, itching and/or rashes. Infusion-associated reactions characterized by chest pain, chest discomfort, chills, tremor, back pain, neck pain, shortness of breath, abdominal pain, fever and headache, fatigue, somnolence that might be

symptoms of hypoxia, have also been observed. If you experience these types of reactions, your doctor may decide to stop or slow the infusion.

Tenkasi may interfere with laboratory tests that measure how well your blood is clotting and may cause a false reading.

While antibiotics, including Tenkasi, fight certain bacteria, they may not be active against other bacteria or fungi, which may, therefore, continue to grow. This is called overgrowth. Your doctor will monitor you in case this happens and treat you if necessary.

After being given Tenkasi, you may get a new infection at another site on your skin. Your doctor should monitor you in case this happens and treat you as necessary.

Children and adolescents

Tenkasi should not be used in children or adolescents below the age of 18.

Other medicines and Tenkasi

Tell your doctor if you are using, have recently used or might use any other medicines.

If you are going to be given a blood thinner called unfractionated heparin, then tell your doctor if you have received Tenkasi within the last 5 days (120 hours).

It is particularly important to tell your doctor if you are using medicines that prevent blood from clotting (oral anticoagulants, e.g. coumarin anticoagulants). Tenkasi may interfere with laboratory tests or self-test that measure how well your blood is clotting (INR) and may cause a false reading up to 12 hours after the infusion.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

You should not be given this medicine during pregnancy unless the benefit is considered to be greater than the risk to the baby.

Driving and using machines

Tenkasi may cause dizziness, which can influence your ability to drive or operate machines.

3. How you will be given Tenkasi

Tenkasi will be given to you by your doctor or nurse, by infusion (drip) into a vein.

The recommended dose for Tenkasi is one single infusion of 1,200 mg administered into a vein over 3 hours.

If you are given more Tenkasi than you should

Your doctor will decide how to treat you, including stopping the treatment and monitoring for signs of ill effects.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse immediately if you experience a reaction to the infusion including any of the following symptoms:

- Flushing of the face and upper body, hives, itching and/or rashes (red man syndrome)
- Wheezing;
- Shortness of breath;
- Swelling around throat or under the skin that develops over a short period of time;
- Shivering or trembling;
- Rapid or weak pulse;
- Chest pain or tightness;
- Decrease in blood pressure (which could make you feel faint or dizzy).

Such reactions may be life-threatening.

Other side effects occur with the following frequencies:

Common side effects (may affect up to 1 in 10 patients):

- Fewer red blood cells or less haemoglobin than normal;
- Feeling dizzy;
- Headache;
- Feeling sick (nausea) or being sick (vomiting);
- Diarrhoea;
- Constipation;
- Pain or irritation where the injection was given;
- Itching, skin rash;
- Muscle pain;
- More enzymes produced by your liver (as shown in blood tests);
- Heart racing or beating fast;
- Infection getting worse or new infection at another site on your skin;
- Swollen, red area of skin or underneath skin that feels hot and tender;
- Accumulation of pus underneath the skin.

Uncommon side effects (may affect up to 1 in 100 patients):

- Higher than normal levels of eosinophils, a type of white blood cell (eosinophilia);
- Low blood sugar;
- High uric acid levels in the blood;
- Increased blood bilirubin levels ;
- Severe rash;
- Flushing;
- Inflammation surrounding a tendon (known as tenosynovitis);
- Bone infection caused by bacteria (known as osteomyelitis);
- Reduced blood platelet count below the normal lower limit (known as thrombocytopenia);
- Abdominal pain
- Chest pain
- Fever
- Shortness of breath

Rare side effects(may affect up to 1 in 1000 patients):

- Headache, fatigue, somnolence that might be symptoms of hypoxia;
- Back pain
- Neck pain
- Chills
- Tremor.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tenkasi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Do not store above 25°C.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment

6. Contents of the pack and other information

What Tenkasi contains

- The active substance is oritavancin. Each vial contains oritavancin diphosphate equivalent to 400 mg oritavancin.
- The other ingredients are mannitol and phosphoric acid.

What Tenkasi looks like and contents of the pack

- Tenkasi is a powder for concentrate for solution for infusion
- Tenkasi is a white to off white powder, supplied in a 50 ml glass vial.
- Tenkasi is available in cartons containing 3 vials.

Marketing Authorisation Holder

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This leaflet was last revised in:

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Tenkasi is intended for intravenous (IV) administration, only after reconstitution and dilution.
Three Tenkasi 400 mg vials need to be reconstituted and diluted to prepare a single once-only 1,200 mg IV dose.

Tenkasi should be prepared under aseptic techniques in a pharmacy.

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 should be clear, colourless to pale yellow solution. Parenteral medicinal products should be inspected visually for particulate matter after reconstitution. Aseptic procedures should be used for the preparation of Tenkasi.

Reconstitution: Aseptic technique should be used to reconstitute three Tenkasi 400 mg vials.

- 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 Tenkasi powder is completely reconstituted in solution.

The reconstituted solution should be further diluted in glucose 5% intravenous infusion bag immediately.

Dilution: Three reconstituted vials are needed for dilution for administration of a single 1,200 mg IV infusion. Only glucose 5% intravenous bag (D5W) should be used for dilution.

To dilute:

- 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.

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 for Tenkasi diluted in glucose 5%

intravenous infusion bag, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.