22 June 2023
EMA/323178/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tenkasi

International non-proprietary name: oritavancin

Procedure No. EMEA/H/C/003785/X/0036

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABSSSI	Acute bacterial skin and skin structure infection
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration; peak plasma concentration
CV%	Coefficient of variation (percent coefficient of variation)
CYP	Cytochrome P450
D5W	Dextrose 5% in water
EC	European Commission
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HPβCD	Hydroxypropyl-β-cyclodextrin
HPLC	high performance liquid chromatography
IRR	Infusion related reaction
ISR	Infusion site reaction
ITT	Intent-to-treat
IV	Intravenous
LC-MS/MS	Liquid chromatography and tandem mass spectroscopy
LLOQ	Lower limit of quantification
MAA	Marketing Authorisation Application
MIC	Minimal inhibitory concentration
mg	milligram
n	Number of subjects
NF	New formulation
NOAEL	No observed adverse effect level
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PopPK	Population pharmacokinetic
QWBA	Quantitative whole-body autoradiography
SAE	Serious adverse event
SD	Single dose
SmPC	Summary of Product Characteristics
SOC	System organ class
SWFI	Sterile water for injection
$T_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TK	Toxicokinetics
T_{max}	Time of maximum drug concentration

T_{min}	Time of minimum drug concentration
µg	microgram
w/v	Weight/volume
w/w	Weight/weight

1. Background information on the procedure

1.1. Submission of the dossier

Menarini International Operations Luxembourg S.A. submitted on 7 March 2022 an extension of the marketing authorisation, to add a new strength of 1200 mg for powder for concentrate for solution for infusion. The RMP (version 4) is updated in accordance.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, point 2 (c) - Extensions of marketing authorisations.

The application submitted is composed of administrative information, quality data, clinical data based on Marketing Authorisation Holder's own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Menarini International Operations Luxembourg S.A. submitted to the EMA an application for modification of the agreed paediatric investigation plan with a deferral as set out in the EMA´s decision P/0498/2021.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig

The application was received by the EMA on	7 March 2022
The procedure started on	24 March 2022
The CHMP Rapporteur's first Assessment Report was circulated to all	13 June 2022

CHMP and PRAC members on	
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 June 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 June 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 July 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	21 July 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	21 December 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	20 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 February 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	23 February 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	24 March 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 April 2023
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the MAH on	26 April 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	19 May 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tenkasi on	22 June 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

At the time of submission of this variation, Tenkasi 400 mg powder for concentrate for solution for infusion is approved for treatment of acute bacterial skin and skin structure infections (ABBSSSI) in adults.

The new formulation (1200 mg powder for concentrate for solution for infusion) is applied for in the same indication.

ABSSSIs include cellulitis/erysipelas, wound infections, major cutaneous abscesses, and burn infections. They commonly involve at least a 75 cm^2 surface area of redness, oedema and/or induration accompanied by lymph node enlargement or systemic symptoms such as fever [FDA, 2010].

The most common bacteria identified in ABSSSI are Gram-positive pathogens, including streptococci and staphylococci.

2.1.2. Epidemiology

ABSSSI are among the most common human bacterial infections and include cellulitis, erysipelas, wound infections (traumatic or post-surgical) and major abscesses. Cellulitis and abscesses are commonly encountered in the community setting and frequently result in hospitalisation. ABSSSI such as surgical site infections and burn infections are also seen in the hospital setting. Both erysipelas and cellulitis are characterised by rapidly spreading areas of oedema, redness, and heat, sometimes accompanied by lymphangitis and enlargement of the regional lymph nodes. ABSSSI are a common indication for antibiotic use in Europe and are associated with considerable morbidity. Data from the European Centre for Disease Prevention and Control (ECDC) estimated that 4% of all healthcare-acquired infections (HAI) reported between 2011 and 2012 were ABSSSI, with surgical-site infections being the second most frequently reported HAI (19.6%) (ECDC, Surveillance report 2011–2012).

In Europe, the most frequently isolated Gram-positive ABSSSI pathogen is *S. aureus* (including methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA)), followed by β-haemolytic streptococci.

The prevalence of MRSA has increased worldwide in both healthcare- and community-based settings. In Europe, the prevalence of MRSA varies greatly across countries, with much higher frequencies seen in southern and south-eastern countries. Based on the European Antimicrobial Resistance Surveillance Network (EARS-Net), the European population-weighted mean percentage for MRSA was 15.5% in 2019, ranging from 1.1% in Norway to 46.7% in Romania (ECDC, Surveillance Report: Antimicrobial resistance in EU/EEA (EARS-Net), 2020).

In particular, in patients with comorbidities and those previously treated with antibiotics, ABSSSI can often be polymicrobial, with Gram-negative and obligate anaerobic pathogens found together with Gram-positive organisms. Gram-negative aetiology is common in surgical-site infections setting as reported in the SENTRY programme (1998 – 2004), with *P. aeruginosa* being the second most important pathogen after MRSA, followed by *E. coli*.

Drug-resistant bacteria are playing an increasing role as causative pathogens in ABSSSI*.* *P. aeruginosa*, *Acinetobacter* species and vancomycin-resistant *Enterococcus* spp. can play an important role in polymicrobial long-standing infections such as diabetic foot infection and decubiti but are also increasingly recognised in monomicrobial ABSSSI. The presence of MRSA in surgical site infections is independently associated with mortality compared with patients with MSSA.

2.1.3. Clinical presentation, diagnosis

No new indication is applied for.

2.1.4. Management

Management of ABSSSI is dependent on the clinical presentation and the severity of the infection. Initial treatment of ABSSSI is usually empirical because culture results are not immediately available, and patients with ABSSSI benefit from rapid initiation of appropriate therapy (Clinical guideline (CG74), NICE 2014). Most streptococci remain susceptible to penicillin and β-lactam antibiotics, providing many treatment options for adults when culture results are known. Infections due to MRSA are more complex in terms of management in hospital because of the additional steps that must be implemented for their treatment (e.g. decolonisation, protective clothing for nurses, isolation units, more expensive antibiotics, frequent laboratory tests, or blood cultures).

When MRSA is identified as a single pathogen, a number of treatment options are available in Europe, including vancomycin, daptomycin, linezolid, tigecycline, tedizolid, oritavancin, dalbavancin, and ceftaroline. Agents like vancomycin, linezolid, and daptomycin have been available for some time. However, these older agents, along with many of the drugs more recently approved for ABSSSI, provide only Gram-positive coverage. In particular, linezolid is one of the most used agents for an empirical starting of the treatment due to its activity against aerobic and anaerobic Gram-positive organisms.

Ceftaroline and tigecycline are active against Gram-negative organisms but are only available in an IV formulation. Cephalosporins, carbapenems (meropenem, imipenem), and ureido-penicillins (such as piperacillin), aminoglycosides, or quinolone antibacterials can be used to provide Gram-negative coverage in these situations, as well. In cases where MRSA and Gram-negative organisms are isolated, these agents can be added to MRSA active agents.

2.2. About the product

The active substance of Tenkasi is oritavancin. Oritavancin is a semi-synthetic lipoglycopeptide antibiotic that has three principal mechanisms of action: 1) inhibition of the transglycosylation (polymerisation) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors; 2) inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall; and 3) disruption of bacterial membrane integrity, leading to depolarisation, permeabilisation, and rapid cell death. These multiple mechanisms contribute to the rapid, concentration-dependent bactericidal activity of oritavancin.

The currently marketed formulation of oritavancin, 400 mg powder for concentrate for solution for infusion, was approved in the EU on 18th March 2015 (EMEA/H/C/003785) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

Oritavancin is dosed as a 1200 mg single intravenous (IV) infusion. The current formulation of oritavancin is packaged as 3 vials, each containing 400 mg of oritavancin and the inactive component mannitol. The vials are reconstituted with sterile water for injection (SWFI) and further diluted in Dextrose 5% in water (D5W) for a total volume of 1000 mL and infused IV over 3 hours.

A new formulation of oritavancin has been developed which utilises the excipient 2-hydroxypropyl-β-cyclodextrin (HPβCD) to improve solubility. The new formulation is packaged as a single vial containing 1200 mg oritavancin, 2400 mg HPβCD, and mannitol. It is reconstituted with SWFI, and further diluted with 0.9% sodium chloride (saline) or D5W for a total volume of 250 mL and infused IV over 1 hour.

The new formulation intends to simplify the preparation of the solution for infusion, reduce the volume of the infusion, shorten the infusion time and give pharmacies flexibility to use either D5W or normal saline (NS) for dilution.

2.3. Type of Application and aspects on development

The MAH submitted an application under article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, point 2 (c).

This application fulfils the CHMP recommendation to explore ways to improve handling or reformulating oritavancin 400 mg by developing a 1200 mg single vial presentation as part of lifecycle management.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing 1200 mg of oritavancin (as oritavancin diphosphate) per vial.

Other ingredients are: hydroxypropylbetadex, mannitol, phosphoric acid, sodium hydroxide.

The product is available in a single-use 50 ml Type 1 glass vial with rubber stopper and aluminium flip off cap as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The active substance, oritavancin diphosphate (INN: oritavancin), is identical to the substance already authorised in Tenkasi 400 mg powder for concentrate for solution for infusion. The active substance's physicochemical properties, synthesis, controls, and stability are fully described in the approved marketing authorisation application for the 400 mg strength. It has a relative molecular mass of 1989.09 g/mol and the following structure:

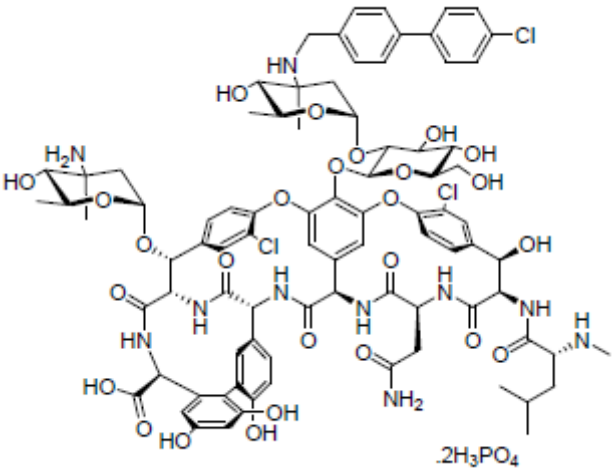


Figure 1: active substance structure

The active substance is a white to pale pink powder. The solubility in water is 60.75 mg/mL; the solubility in buffers depends on nature of buffer and pH, with reduced solubility at neutral pH (e.g. 0.42 mg/mL in

phosphate buffer at pH 7.0). The partition coefficient is -0.64 indicating poor lipophilicity. The substance is hygroscopic.

Since the substance is dissolved during the manufacturing process of the finished product, particle size distribution and polymorphism are not relevant quality attributes to control or test.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a lyophilised, solid white to off white or pink cake or powder packaged in a 50 mL Type I glass vial with rubber stopper and aluminium flip-off cap.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The approved 400 mg/vial formulation requires three vials to reconstitute and administer the 1200 mg dose. The new formulation of 1200 mg/vial requires only one vial per dose. In this new formulation, hydroxypropylbetadex (HPβCD), a betacyclodextrin derivatised with propylene oxide, was added as an additional excipient to enhance the solubility and stability of oritavancin at neutral pH and in isotonic media. The 1200 mg formulation will be manufactured by the same manufacturer as Oritavancin 400 mg, by the same process, with slight changes to accommodate the new excipient, and will have the same primary container closure system as the 400 mg formulation.

While the 400 mg formulation is incompatible with standard saline infusion solution, the new 1200 mg formulation allows the use of saline solution for infusion. The 400 mg formulation is reconstituted with sterile WFI, further diluted in glucose 5 % in water (D5W) for a total volume of 1000 mL and infused intravenously over 3 hours. The new formulation is presented as a single vial which will be reconstituted with sterile WFI and further diluted with 0.9 % sodium chloride or D5W for a total volume of 250 mL and infused intravenously over 1 hour only. Thus, the new formulation allows administration of a higher concentration (4.8 mg/mL instead of 1.2 mg/mL) in a shorter period of time (one hour instead of three hours with the 400 mg formulation), with a lower infusion rate (4.167 mL/min versus 5.55 mL/min with the 400 mg formulation). Clinical pharmacology studies demonstrated that comparable systemic exposure and tissue distribution are observed for both the old and new formulations and methods of administration.

The formulation used during clinical studies is the same as that intended for marketing.

The use of sterile filtration followed by aseptic processing as manufacturing process for the applied finished product is sufficiently justified as other sterilisation methods resulted in extensive degradation of oritavancin. The applied sterile filtration approach is supported by filter compatibility studies and media fills.

Studies demonstrated absence of risk for leachables from the rubber stoppers.

The primary packaging is a 50 mL Type I glass vial with rubber stopper and aluminium flip-off cap. The materials comply with Ph. Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of eight main steps: dispensing, compounding, bioburden reduction filtration, aseptic filtration through 2 sterilizing filters, filling of vials and partial stoppering, lyophilisation and stoppering, capping, and visual inspection. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

The process has been fully validated by three full scale batches.

Holding times were adequately addressed and validated during process validation.

2.4.3.3. Product specification

The finished product release specification include appropriate tests for this kind of dosage form: appearance (visual), reconstitution time (visual), visible particulates (visual), color and clarity of solution (Ph. Eur.), identity (HPLC, UV), assay and impurities (HPLC), uniformity of dosage units (Ph. Eur.), water content (Karl Fischer), residual ethanol (GC), pH (Ph. Eur.), particulate matter (Ph. Eur.), bacterial endotoxins (Ph. Eur.), and sterility (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Ethanol is used in the manufacturing of active substance, and residual ethanol is present in the active substance at a level above the ICH Q3C limit. The lyophilisation step in the finished product manufacturing process ensures the residual ethanol in the finished product is reduced to a level below the ICH Q3 limit, which is also controlled in the finished product at release.

During the procedure, a MO was raised to which the company responded by tightening certain impurity limit and by reintegration of stability chromatograms.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for six full scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three full scale batches of finished product stored for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

During the procedure, a MO was raised to which the company responded by updating appropriately the stability data package.

Samples were tested for appearance, reconstitution time, visual particulates, particulate matter, pH, water content, assay of oritavancin and impurities, sterility and bacterial endotoxins. The analytical procedures used are stability indicating.

Some impurities showed a slight increase over time, but remained well within specifications, and are not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC. The other parameters tested showed no trends.

Photostability studies were conducted according to ICH Q1B for the Oritavancin 400 mg formulation. The molecule was demonstrated to be stable in the clear glass vial without label and not to be light-sensitive. Consequently, no special packaging protection from light is needed.

No additional photostability studies were performed on the new 1200-mg formulation, since the MAH assumed that the increase in active substance per vial, the more neutral pH, and the addition of the new HPβCD excipient will not affect photostability. This rationale was accepted by CHMP.

In-use stability demonstrated that the reconstituted and diluted solution is physically and chemically stable for 48 hours at 25°C. From a microbiological point of view, the finished 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 4 hours at 25 °C and 12 hours at 2 °C -8 °C following dilution in a glucose 5% or sodium chloride 0.9% intravenous infusion bag.

Based on available stability data, the proposed shelf-life of 48 months with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Oritavancin is newly formulated with 1200 mg in each vial to improve the handling of this substance. The new formulation utilizes the excipient hydroxypropyl-β-cyclodextrin (HPβCD, hydroxypropyl betadex) to improve the solubility. Nevertheless, oritavancin NF is formulated to deliver the same dose of oritavancin as the currently approved formulation and is administered for the same indication.

Therefore, the non-clinical program is amended by three studies to support comparability to the current formulation in addition to two corresponding method validations, as well as literature-based safety information for the excipient hydroxypropylbetadex (HPβCD).

Study-ID	Title	GLP
Pharmacokinetics		
0017-3571	Validation of a HPLC/MS detection method for the determination of oritavancin in Sprague Dawley rat plasma (K_2EDTA)	Yes
0017-3560	Validation of a HPLC with UV detection method for the determination of oritavancin in 5% dextrose and 1% HPβCD in 5% dextrose	Yes
00843501	A pharmacokinetic and tissue distribution study of [^{14}C]-Oritavancin following a 60 min IV infusion administration to male and female rats	Yes
Toxicology		
SR15-030	Pharmacokinetics and single dose toxicology of oritavancin formulated in D5W or HPβCD following a 1-hour infusion in Sprague Dawley rats.	No
1017-3581	Oritavancin: a 28-day IV infusion toxicity study followed by a 14-day recovery period in Sprague Dawley rats	Yes

These studies and literature data for HPβCD are focussed in this assessment and older data from the initial MAA are still applicable and only discussed in context if necessary.

2.5.2. Pharmacology

No new primary, secondary, or safety pharmacology studies were conducted to support this application.

2.5.3. Pharmacokinetics

Two new GLP bioanalytical method studies (0017-3571 and 0017-3560) were developed to support the 28-day repeat dose toxicity study comparing the toxicity and TK of oritavancin in D5W with oritavancin in HPβCD. Both methods met the defined validation requirements.

Comparative absorption for both formulations was analysed after single dose and 4-weeks daily intravenous 1-hour infusion in rats. Similar to the findings in the previously conducted ADME studies for oritavancin 400 mg, the new studies for oritavancin NF exhibited linear, dose proportional plasma kinetics with maximal levels attained at the first sampling time point after the end of infusion. There were no gender differences in the PK among the different species in repeat dose studies and there was no plasma accumulation of oritavancin following multiple dosing.

Tissue distribution was analysed in a GLP QWBA study (00843501) in rats. Formulations of [14C]-oritavancin were administered as a single 60-minute IV infusions to male and female Sprague Dawley rats at 20 mg/kg and a target radioactivity of 100 µCi/kg in both vehicles. Overall, the oritavancin tissue distribution pattern was similar in this study to the previously conducted QWBA studies. In addition, no significant differences with respect to oritavancin distribution were identified between the two vehicles. The slower administration over 1 hour did not result in a different tissue distribution in comparison to the previous faster bolus injections. Only at one time-point, the oritavancin concentration in the eye was slightly above the LLOQ (527 ng equiv./g) in the new formulation in the analysed male and female while not detectable in the eyes of the corresponding DW5 treated animals. The presence of HPβCD at a 2:1 w/w ratio to oritavancin, the same as in the clinical formulation, produced no substantive differences in oritavancin exposure, accumulation, tissue distribution, or elimination.

No new studies for oritavancin metabolism and excretion were conducted.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

A comparative non-GLP single dose study with 1-hour infusion to compare pharmacokinetics and toxicity of oritavancin formulated in D5W and HPβCD (4:1 w/w ratio of HPβCD : oritavancin) was conducted in Sprague-Dawley rats. The final doses (50 and 100 mg/kg) were reached by dilution in D5W. A final concentration of 10 mg/mL (50 mg/kg dose with 4% HPβCD) and 20 mg/mL (100 mg/kg dose with 8% HPβCD) was used.

The corresponding PK data indicate that the formulation did not have an impact on the pharmacokinetics of oritavancin. The NOAEL was determined at the highest dose.

2.5.4.2. Repeat dose toxicity

In a 28-day comparative GLP repeat-dose toxicity study in rats a once daily 60-minute IV infusion of the current D5W or the new HPβCD in D5W formulation including respective vehicle controls was analysed for toxicity and corresponding oritavancin toxicokinetics. The analysed HPβCD formulation in the study was similar to the applied clinical formulation for humans, in a 2:1 w/w ratio of HPβCD to oritavancin. Three doses, vehicle controls, 5, 15 and 50 mg/kg/d were analysed for both formulations. The NOAEL was concluded at the mid-dose of 15 mg/kg/d due to the low severity and incidence of the observed findings. In general, all findings (hematology, liver, kidney, GI tract) were similar for Oritavancin D5W (current formulation) and Oritavancin HPβCD (Oritavancin NF) except for HPβCD-related findings in the kidney. Minimal to moderate renal tubular changes, consisting of increased tubular rarefaction (pallor) accompanied by small segments of tubular vacuolar degeneration occurred in all HPβCD-treated animals including the respective vehicle controls. The kidney changes in the Oritavancin NF treated animals did not result in differences of renal function, as the extent of the

increase of serum urea and creatinine or the changes in urinary parameters did not differ between the animals treated with the different vehicles and formulations.

2.5.4.3. Genotoxicity

No new genotoxicity studies have been conducted.

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been conducted.

2.5.4.5. Reproductive and developmental toxicity

No new reproductive and developmental toxicity studies have been conducted.

2.5.4.6. Toxicokinetic data

The relative plasma exposure (oritavancin in HPβCD/oritavancin D5W) ranged from 0.812 - 1.31 for C_{max} and from 0.841 - 1.29 for AUC (last) in the 28-day repeat-dose toxicity study and is therefore considered equivalent in rats. No HPβCD plasma levels were determined in this study.

2.5.4.7. Tolerance

No new local tolerance studies have been conducted. Local tolerance endpoints were included into the comparative 28-day repeat-dose toxicity. No evidence that the formulation containing HPβCD produced significant or enhanced adverse effects at the injection site was found beyond the usual procedure related local findings that were also recognised in control groups.

2.5.4.8. Other toxicity studies

The MAH summarized the known non-clinical data for HPβCD from the literature. The respective literature references are listed in the non-clinical AR.

Safety pharmacology

No effects were observed on mean arterial blood pressure, heart rate, QRS duration, QT interval, or cardiac tissue damage when compared to dextrose-treated controls after total IV doses of 62.85 and 251.4 mg/kg in Wistar rats.

At high doses (200, 400, and 800 mg/kg) of HPβCD administered by intravenous infusion to anesthetized Beagle dogs produced increased renal arteriolar resistance and decreased renal blood flow, more prominently in females than males, without impact on pulmonary hemodynamic parameters or cardiac electrophysiology. However, an increase in mean blood pressure, associated with a reflex decrease in heart rate, was observed at the highest dose, with significant effects on those parameters observed in females only.

Single-Dose Toxicity

A single IV dose of 2250 mg/kg HPβCD was reported to be lethal to rats, however when the dose was reduced to 1000 mg/kg, no deaths or adverse clinical signs were observed.

A single IV dose of 2 g/kg or 10 g/kg HPβCD given to cynomolgus monkeys was reported not to be lethal.

Repeat-Dose Toxicity

Repeated IV administration of HPβCD in animals was generally well tolerated when administered at doses of up to 400 mg/kg/day.

Rats administered HPβCD at a dose of 225 mg/kg / day by continuous infusion for 4 or 7 days exhibited histopathological changes including foamy macrophage infiltration of the lungs, with some associated alveolitis, haemorrhage, and atelectasis. Renal cortical tubular vacuolation of the proximal convoluted tubules and mild reduced splenic extramedullary haematopoiesis were also seen. Reversible vacuolation of renal tubular epithelium cells was the primary effect observed in repeat-dose toxicity studies, without evidence of deterioration of renal function or histopathological evidence of kidney toxicity.

Two 3-month IV toxicity studies were conducted in rats and dogs at doses of 50, 100, or 400 mg/kg/day. In rats, the NOAEL was 50 mg/kg/day. At 100 mg/kg/day, there were minimal histological changes (swollen epithelial cells) in the bladder, swollen and granular kidney tubular cells, and an increase in Kupffer cells in the liver. At 400 mg/kg/day, there were decreases in body weight and food consumption, increased water consumption, decreased haematocrit, haemoglobin, and erythrocyte levels, and increased creatinine, total bilirubin, and aspartate and alanine aminotransferase levels. Increases in spleen, adrenal, and kidney weights, along with histopathological changes in lungs (foamy cells), spleen, and liver were also seen at this dose level. These changes were reversible after one month, with the exception of small elevations in AST and ALT and partial reversal of urinary tract bladder and lung findings.

In dogs administered IV doses of 50, 100, or 400 mg/kg for 3 months, the NOAEL was 100 mg/kg/day. At 400 mg/kg/day, there were slight increases in plasma liver enzymes and foamy cells in lung and swollen epithelial cells of the bladder and renal pelvis. All changes were reversible after one month except for incomplete reversibility of swollen renal pelvis epithelium.

Genotoxicity

HPβCD was reported to be negative in an Ames assay at levels up to 1000 g/plate and in an in vivo micronucleus assay at doses up to 5000 mg/kg/day. In addition, HPβCD was reported to be negative in an unscheduled DNA synthesis assay, a mouse lymphoma assay, and a human lymphocyte chromosome aberration assay.

Reproductive and Developmental Toxicity

In rats dosed throughout the period of organogenesis (gestation day 6 - 16), intravenous doses of 400 mg/kg/day HPβCD produced slight maternal toxicity but no adverse effects in offspring. No adverse effects were observed in rabbits given IV doses of up to 400 mg/kg/day. In rats given oral doses of 500, 200, and 5000 mg/kg/day, no maternal toxicity, embryotoxicity, or teratogenicity were observed. Rabbits dosed orally at 1000 mg/kg/day exhibited slight maternal and embryotoxicity but no evidence of teratogenicity.

Similarly, oral doses of HPβCD at levels of 500 or 1000 mg/kg/day were reported to produce no effects on rat fertility and no evidence of teratogenicity in rats or rabbits. Evidence of maternal toxicity was observed in rabbits at both dose levels.

2.5.5. Ecotoxicity/environmental risk assessment

The present extension application to add a new strength without changing the recommended maximum daily dose of 1,200 mg will not lead to an increased predicted environmental concentration compared to the initial environmental risk assessment. Hence, the initial environmental risk

assessment submitted with the MAA is still valid and an update is considered not necessary.

2.5.6. Discussion on non-clinical aspects

The MAH stated that no additional new nonclinical pharmacology studies were conducted because the newly conducted studies described above indicated that the extent of the systemic exposure, the organ distribution pattern and the observed toxicity of the current oritavancin formulation and oritavancin NF were comparable, indicating that HPβCD will not change the already established pharmacodynamics activity and the safety pharmacology profile of oritavancin. This view is supported.

The main focus on this application was further to clarify if the new formulation that includes HPβCD has any impact on the overall (PK) pharmacokinetics of oritavancin since oritavancin PK is known from the initial MAA for the 400 mg formulation in D5W.

In general, no significant differences with respect to absorption, elimination, accumulation, and tissue distribution were observed for both formulations (D5W and HPβCD). Only at one time-point in the rat QWBA study, the oritavancin concentration in the eye was slightly above the LLOQ (527 ng equiv./g) in the new formulation in the analysed male and female while not detectable in the eyes of the corresponding DW5 treated animals. This small difference is considered of negligible overall relevance due to the short duration and low concentration. The oritavancin tissue distribution pattern was further similar in this study to the previously conducted QWBA studies.

No new studies for oritavancin metabolism and excretion were conducted as cyclodextrins are known to have no impact on metabolism and excretion. Drug dissociation due to dilution is the major release mechanism. The drug is not changed and metabolism and excretion follow the same routes.

The original oritavancin nonclinical program evaluated single dose toxicity in rats, repeat dose toxicity in rats and dogs, genotoxicity in vitro and in vivo studies, reproductive and developmental toxicity in rats and rabbits, juvenile animal toxicity in rats and dogs, and because oritavancin accumulates in macrophages, a series of in vitro studies were conducted in macrophage cell lines and in vivo studies were conducted in rats to evaluate immune function. Since these data evaluated the overall non-clinical safety for oritavancin. As the final oritavancin dose is not changed by the new formulation (Oritavancin NF) only comparative studies, one single dose and one 28-day repeat-dose toxicity study, to analyse the differences between both formulations (D5W and HPβCD) were conducted to analyse toxicity and toxicokinetic of both formulations. This approach is supported.

Due to the slower infusion time (1 hour) no toxicity for oritavancin was observed in the comparative non-GLP SD study in rats at doses of 50 and 100 mg/kg in both formulations. In addition, no differences in toxicokinetic and PK parameters were observed. In contrast, the initially conducted SD toxicity study with 1.5 to 2 minutes bolus injections in rats elicited pronounced overall toxicities in addition to mortality at doses in a similar range (40, 80, 120 mg/kg).

In a 28-day comparative GLP repeat-dose toxicity study in rats a once daily 60-minute IV infusion of the current D5W or the new HPβCD in D5W formulation including respective vehicle controls was analysed for toxicity and corresponding oritavancin toxicokinetic. The analysed HPβCD formulation in the study was similar to the applied clinical formulation for humans, in a 2:1 w/w ratio of HPβCD to oritavancin. Three doses, vehicle controls, 5, 15 and 50 mg/kg/d were analysed for both formulations. The NOAEL was concluded at the mid-dose of 15 mg/kg/d due to the low severity and incidence of the observed findings. In general, all findings (haematology, liver, kidney, GI tract) were similar for Oritavancin D5W (current formulation) and Oritavancin HPβCD (Oritavancin NF) except for HPβCD-related findings in the kidney. Minimal to moderate renal tubular changes, consisting of increased tubular rarefaction (pallor) accompanied by small segments of tubular vacuolar degeneration occurred

in all HPβCD-treated animals including the respective vehicle controls. The kidney changes in the Oritavancin NF treated animals did not result in differences of renal function, as the extent of the increase of serum urea and creatinine or the changes in urinary parameters did not differ between the animals treated with the different vehicles and formulations. These changes are an expected finding with IV dosing of HPβCD in rats (Gould and Scott, 2005), they are not associated with changes in kidney function, as also confirmed here. Therefore, the MAH concludes that these findings do not reflect a risk to human safety in patients treated with a single dose of oritavancin NF.

According to the Report published in support of the 'Questions and answers on cyclodextrins used as excipients in medicinal products for human use' (EMA/CHMP/495747/2013), HPβCD can be found in marketed parenteral formulations with intravenous dosing up to 16 g daily in itraconazole formulations. No side effects were observed in humans after parenteral administration of up to 24 g of HPβCD daily for 15 days (Loftsson, T., Brewster, M.E., 'Pharmaceutical applications of cyclodextrins: basic science and product development', J. Pharmacy and Pharmacology, Vol. 62, 2010, p. 1607-1621). As Tenkasi 1200 mg (Oritavancin NF) is given as a single administration this would result in a total dose of 2400 mg per person, which is nevertheless well below the already marketed dose of 16 g HPβCD.

Of greater relevance, HPβCD-related kidney findings did not worsen the changes of renal function induced by oritavancin, as the extent of the increase of serum urea and creatinine or the changes in urinary parameters observed in high dose groups were similar regardless the vehicle. Therefore, no increased renal toxicity is expected by a combination of HPβCD and oritavancin.

At the NOAEL of the 28-day repeat-dose toxicity study no safety margins for oritavancin exposure are available as the exposure is almost similar. However, since oritavancin related toxicity was not changed by HPβCD in rats and this does not translate into a different conclusion on oritavancin safety.

The non-clinical safety of HPβCD was thoroughly discussed by the MAH with a respective discussion of the available literature. Comparatively low concentrations of HPβCD are included in Oritavancin NF and oritavancin is further dosed as a single administration while other parenteral formulations for repeated infusions included higher doses HPβCD of per day. Therefore, and in addition to the known findings of the repeat-dose study, no change in the safety profile of the new formulation is expected.

It can be expected that the addition of a new strength will not pose a risk to the environment when used in accordance with the Product Information.

2.5.7. Conclusion on the non-clinical aspects

The existing non-clinical program for oritavancin was bridged by pharmacokinetics and single and repeat-dose toxicity studies in rats which revealed no significant differences with respect to oritavancin in the new formulation. HPβCD-related known findings in kidneys were identified at comparatively low concentrations in the 28-day repeat-dose toxicity study but did not result in differences of renal function in comparison to the old formulation. This information has been included in the SmPC and an increased safety risk is not expected from these non-clinical data.

2.6. Clinical aspects

2.6.1. Introduction

Two studies were conducted, Study MDCO-ORI-15-01 and Study ML-ORI-102, which encompass 90 subjects treated with the new formulation of oritavancin. These studies were designed to collect the

necessary pharmacokinetic (PK) data to compare the new oritavancin formulation with the current approved formulation, while also collecting key safety data.

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

2.6.2. Clinical pharmacology

Table 1: Clinical studies conducted with the new 1200 mg oritavancin formulation

Study ID	Study design	Subjects	Dosing Regimen	Total number of subjects enrolled/completed
MDCO-ORI-15-01	Randomised, double-blind, single-centre, cohort study	Healthy male and female subjects	Single IV dose of oritavancin 400 mg formulation or 1200 mg new formulation over 0.5 h to 3 h; placebo	56 subjects enrolled 55 subjects completed
ML-ORI-102	Randomised, open-label, multi-centre study	Patients with ABSSSI	Single IV dose of oritavancin 400 mg formulation or 1200 mg new formulation over 3 h or 1 h	102 subjects enrolled 99 subjects completed

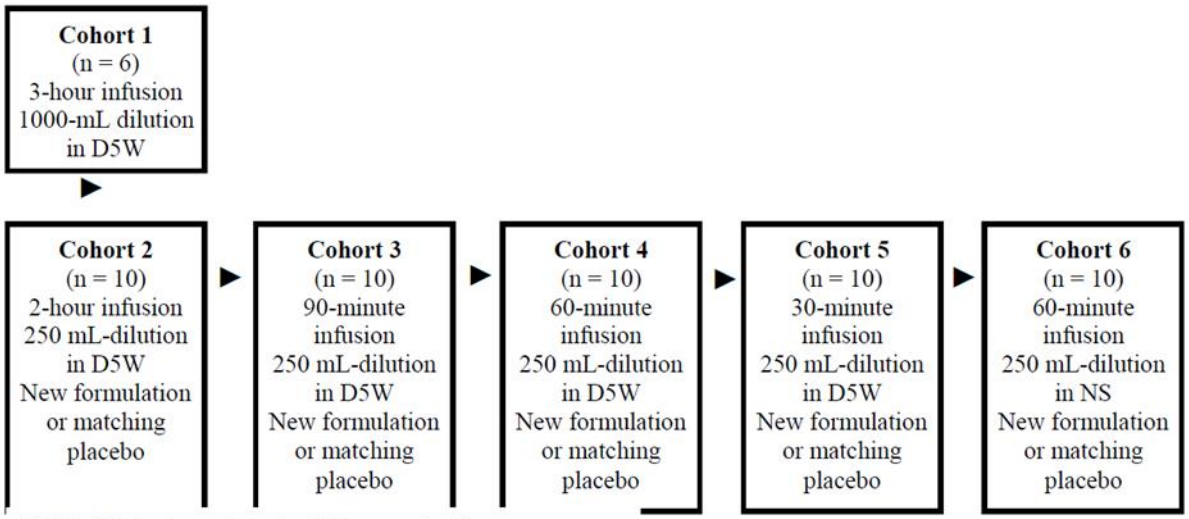
2.6.2.1. Pharmacokinetics

Absorption

Study MDCO-ORI-15-01

This was a Phase 1, single-centre, double-blind study to evaluate the pharmacokinetics and safety of a single 1200 mg IV infusion of the new oritavancin formulation in healthy adult subjects.

For this, 56 subjects were enrolled and assigned to the following 6 cohorts:



D5W: 5% dextrose in water; NS: normal saline

Within Cohort 1, all subjects were assigned to receive oritavancin. Within Cohorts 2, 3, 4, 5, and 6, subjects were randomly assigned to treatment in a ratio of 4:1 to receive oritavancin or placebo (8 subjects on oritavancin, and 2 subjects on placebo).

Subjects had blood collected for oritavancin plasma concentration analyses prior to the start of dosing (0 hours) and at the end of the infusion (either at 3 or 2 hours, or at 90, 60, or 30 minutes), and at 3, 9, 21, 45, 69, and 165 hours after the completion of the infusion.

Results

All 46 subjects who received a dose of oritavancin were included in the PK analysis. The results are shown in Table 2.

For Cohort 1, using the currently approved formulation and an infusion duration of 3 hours, the mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values (3278 and 3537 h*μg/mL, respectively) were higher (approximately 1.2- to 1.4-fold) than the AUC values for all other cohorts. The mean $t_{1/2}$, Vz, and CL were shorter or lower (approximately 0.5- to 0.9-fold) for Cohort 1 compared with all other cohorts.

For Cohorts 2 through 5 (oritavancin new formulation diluted in D5W), mean C_{max} estimates were 152.5, 176.8, 201.9, and 199.1 µg/mL, respectively, as the duration of infusion decreased across these cohorts (2 hours, and 90, 60, and 30 min, respectively). Mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values were similar across Cohorts 2 through 5, ranging from 2377 hr*µg/mL to 2807 hr*µg/mL for $AUC_{0\text{-last}}$ and 2617 hr*µg/mL to 3063 hr*µg/mL for $AUC_{0\text{-inf}}$. Mean $t_{1/2}$, CL, and Vz were also comparable between Cohorts 2 through 5.

For Cohort 6, in which the oritavancin new formulation was diluted in NS and infused over 60 min, mean C_{max} was 205.8 µg/mL, and mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values were 2719 and 2962 hr*µg/mL, respectively. These values were comparable to the results for the same PK parameters for Cohort 4, in which the infusion duration was also 60 min (mean C_{max} 201.9 µg/ml, mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$, 2535 and 2756 hr*µg/mL, respectively).

Table 2: Summary of mean (CV%) oritavancin PK parameters by cohort (PK population; n =46); study MDCO-ORI-15-01

PK Parameter (units)	Cohort 1 (n = 6)	Cohort 2 (n = 8)	Cohort 3 (n = 8)	Cohort 4 (n = 8)	Cohort 5 (n = 8)	Cohort 6* (n = 8)
IV infusion duration:	3 hours	2 hours	90 minutes	60 minutes	30 minutes	60 minutes
$AUC_{0\text{-last}}$ (h*µg/mL)	3278 (18.6)	2377 (22.7)	2509 (29.0)	2535 (32.2)	2807 (14.7)	2719 (20.5)
$AUC_{0\text{-inf}}$ (h*µg/mL)	3537 (16.7)	2617 (23.9)	2727 (28.0)	2756 (31.1)	3063 (14.3)	2962 (20.7)
C_{max} (µg/mL)	182.8 (11.4)	152.5 (17.5)	176.8 (15.5)	201.9 (20.5)	199.1 (11.8)	205.8 (7.3)
T_{max} (h)	3.040 (3.00-3.08)	2.000 (2.00-2.02)	1.465 (1.44-1.51)	1.025 (1.00-1.04)	0.490 (0.48-0.51)	0.970 (0.96-1.00)
$t_{1/2}$ (h)	47.807 (32.6)	60.694 (14.6)	61.264 (21.7)	62.968 (24.7)	57.479 (14.7)	52.608 (19.5)
CL (L/h)	0.3483 (18.6)	0.4871 (29.0)	0.4729 (29.3)	0.4783 (33.7)	0.3988 (14.2)	0.4238 (24.9)
V_z (L)	24.00 (40.7)	42.13 (26.0)	42.01 (36.1)	45.63 (57.9)	33.24 (24.4)	32.49 (32.9)

Source: Section 14.2 Table 14.2.2
Cohort 1: 1200 mg of oritavancin diluted in 1000 mL of 5% dextrose in water (D5W).
Cohort 2: 1200 mg of oritavancin diluted in 250 mL of D5W with hydroxypropyl-β-cyclodextrin (HPβCD) or placebo of 250 mL of D5W.
Cohort 3: 1200 mg of oritavancin diluted in 250 mL of D5W with HPβCD or placebo of 250 mL of D5W.
Cohort 4: 1200 mg of oritavancin diluted in 250 mL of D5W with HPβCD or placebo of 250 mL of D5W.
Cohort 5: 1200 mg of oritavancin diluted in 250 mL of D5W with HPβCD or placebo of 250 mL of D5W.
*Cohort 6 differs from Cohort 4 as this cohort administered a 60-minute infusion diluted in 250 mL of normal saline (NS) instead of D5W.
Note: T_{max} reported as median (minimum-maximum).
CV%: percent coefficient of variation; h: hour(s); IV: intravenous; PK: pharmacokinetic

Distribution

Oritavancin distributes widely into tissue.

Elimination

Oritavancin is not metabolised and is slowly excreted unchanged in faeces and urine.

Dose proportionality and time dependencies

Oritavancin exhibits linear PK at doses up to 1200 mg. Oritavancin does not demonstrate time-dependent PK.

Pharmacokinetics in target population

Study ML-ORI-102

This was a randomised, open-label, multi-centre study in adult subjects who had a diagnosis of ABSSSI (wound infection, cellulitis/erysipelas, or cutaneous abscess) suspected or confirmed to be caused by a Gram-positive pathogen. One-hundred-two (102) subjects were enrolled and randomly assigned in a 1:1 ratio to the current approved formulation or the new formulation.

Subjects randomised to the current approved formulation received 1200 mg oritavancin reconstituted in SWFI and further diluted in D5W to a final volume of 1000 mL, infused over 3 hours. Subjects randomised to the new formulation received 1200 mg oritavancin reconstituted with SWFI and further diluted in 0.9% sodium chloride to a final volume of 250 mL, infused over 1 hour.

Blood samples for the analysis of oritavancin in plasma were collected on Day 1 pre-dose and at the end of infusion (1 hour or 3 hours), and then at 3 hours (for 1 hour infusion), 6 hours, 12 hours, 24 hours, 72 hours, and 168 hours after the start of the infusion.

Results

One-hundred (100) subjects were included in the PK population (two subjects did not complete the study drug infusion and therefore did not have post-baseline PK samples collected). The oritavancin PK parameter are summarised in Table 3.

Due to the shorter infusion time, the mean oritavancin C_{max} was approximately 1.32-fold higher following administration of the new formulation as compared to the currently approved oritavancin formulation. Consistently, the mean time to reach C_{max} was also lower with the new formulation than the currently approved formulation (1.21 hours vs. 3.37 hours).

Mean AUC_{0-72} was 1470 h*μg/mL for the currently approved formulation, compared to 1460 h*μg/mL for the new formulation. Mean AUC_{0-168} was 1760 h*μg/mL for the currently approved formulation, compared to 1750 h*μg/mL for the new formulation (Table 3).

Table 3: Summary of mean (CV%) oritavancin PK parameter (PK analysis set); study ML-ORI-102

PK Parameter (units)	Current Approved N=50 Mean (CV%)	New N=50 Mean (CV%)
IV Infusion Duration	**3 hours**	**1 hour**
AUC_{0-last} (h*µg/mL)	1740 (41.7)	1730 (35.2)
AUC_{0-inf} (h*µg/mL)	1880 (41.3)	1870 (34.8)
AUC_{0-72} (h*µg/mL)	1470 (39.7)	1460 (35.1)
AUC_{0-168} (h*µg/mL)	1760 (41.4)	1750 (35.0)
C_{max} (µg/mL)	112 (30.8)	148 (29)
T_{max} (h)	3.37 (13.1)	1.21 (28.3)
$t_{1/2}$ (h)	43.6 (30.8)	44.4 (29.9)
CL (L/h)	0.764 (54.4)	0.751 (53.9)
V_{ss} (L)	33.3 (90.6)	31.7 (78.1)

Abbreviations: AUC_{0-inf} = area under the plasma concentration-time curve from 0 to infinity; AUC_{0-last} = area under the plasma concentration-time curve from 0 to last quantifiable time point; CL = total body clearance; C_{max} = maximum plasma concentration (observed); CV = coefficient of variation; IV = intravenous; PK = pharmacokinetics; $t_{1/2}$ = terminal half-life; T_{max} = time to maximum plasma concentration (observed); V_{ss} = volume of distribution at steady state
Source: PK Analysis Report Table 10-3 and Table 10-4

The geometric mean ratios of AUC_{0-72} and AUC_{0-168} were within the range of 80% to 125% (109.6% for AUC_{0-72}, 106.6% for AUC_{0-168}). However, the upper limit of the 90% CI for AUC_{0-72} was slightly outside the bioequivalence interval (Table 4).

Table 4: Relative AUC exposure evaluation of currently approved vs. new formulation of oritavancin following a single 1200 mg IV infusion in ABSSSI patients; study ML-ORI-102

	Least Squares Geometric Mean		Percent Ratio of Geometric Mean (%)	Percent Ratio of Geometric Mean 90% CI
PK Parameter	Reference	Test	Test/Reference	Test/Reference
$AUC_{0\text{-}72}$ (h*µg/mL)	1288.6	1411.9	109.6	95.0-126.3
$AUC_{0\text{-}168}$ (h*µg/mL)	1581.0	1684.8	106.6	92.3-123.0

Abbreviations: AUC = area under the curve; CI = confidence interval; IV = intravenous; PK = pharmacokinetic; Reference = oritavancin current approved formulation; Test = oritavancin new formulation.
Source: PK Analysis Report Table 10-1

Special populations

Impaired renal function

The new formulation relies on HPβCD a modified cyclodextrin which is renally excreted. Thus, clearance of HPβCD may be reduced in patients with renal impairment. See section on clinical safety for further discussion.

2.6.2.2. Pharmacodynamics

Not applicable since no new data have been submitted.

2.6.3. Discussion on clinical pharmacology

During the assessment of the initial Marketing Authorisation Application, the CHMP highlighted that the combination of three vials bears a risk of contamination during handling and the MAH was requested to explore ways to improve handling or reformulating oritavancin 400 mg by developing a 1200 mg vial presentation as part of lifecycle management.

Thus, the applied new oritavancin formulation was developed to deliver the same dose as the currently approved 400 mg oritavancin formulation and to be administered for the same indication.

To support the application, two Phase 1 studies were conducted to compare PK data of the new formulation with the currently approved formulation in healthy subjects and patients with ABSSSI.

In healthy subjects, oritavancin exposure was lower with the new formulation compared to the currently approved 400 mg formulation. However, in the target population exposures were similar and comparable to PK data of ABSSSI patients included in the two Phase 3 studies SOLO I & II conducted with the currently approved formulation. Since the AUC/MIC ratio of oritavancin correlates best with efficacy, it would be expected that the new formulation has a similar efficacy as the currently approved formulation. Moreover, Cmax values in ABSSSI patients from study ML-ORI-102 and the Phase 3 studies SOLO I & II conducted with the currently approved formulation were comparable.

The results of study ML-ORI-102 are reflected in section 5.2 of the SmPC of both formulations.

2.6.4. Conclusions on clinical pharmacology

The exposure of the currently approved oritavancin formulation (1200 mg dissolved in a total volume of 1000 ml) infused over 3 hours was comparable to the new oritavancin formulation (1200 mg

dissolved in a total volume of 250 ml) administered over 1 hours in patients with ABSSI.

2.6.5. Clinical efficacy

Not applicable, since no new efficacy data have been submitted.

2.6.6. Clinical safety

Study MDCO-ORI-15-01

In this study 46 healthy subjects received a single 1200 mg dose of oritavancin, 6 subjects the currently approved formulation and 40 subjects the new formulation (for description of the study see section 3.3.1.1).

Overall, 10 subjects (17.9%) reported at least 1 TEAE and 8 subjects (14.3%) reported a TEAE considered related to study drug. There were no deaths, SAEs, or TEAEs leading to study drug or study discontinuation. All TEAEs were mild in severity.

A higher percentage of subjects (4 subjects, 50.0%) reported TEAEs in Cohort 3 (90-minute IV infusion) followed by subjects (3 subjects, 37.5%) in Cohort 4 (60-minute IV infusion). Similar percentages of subjects reported TEAEs considered related to study drug in Cohorts 3 and 4 (3 subjects each, 37.5%). No TEAEs were reported by subjects in Cohort 1 (3-hour IV infusion) or Cohort 2 (2-hour IV infusion). There was no evidence of an increase or change in TEAEs with a decrease in infusion time in Cohorts 1 through 5 and no evidence of a response to switching to NS between Cohorts 4 and 6.

A summary of TEAEs by SOC with a reasonable possibility of being study related is presented in Table 7. Overall, TEAS reported by more than one subject and with a reasonable possibility of being related to study drug were diarrhoea, oral paraesthesia and headache (2 subjects each, 3.6%).

Table 5: Summary of treatment-emergent adverse events with a reasonable possibility of being related to study drug by system organ class and preferred term (safety population); study MDCO-ORI-15-01

System Organ Class Preferred Term	Cohort 1 (3-hour IV) (n = 6) n (%)	Cohort 2 (2-hour IV) (n = 8) n (%)	Cohort 3 (90-min IV) (n = 8) n (%)	Cohort 4 (60-min IV) (n = 8) n (%)	Cohort 5 (30-min IV) (n = 8) n (%)	Cohort 6* (60-min IV) (n = 8) n (%)	Placebo (n = 10) n (%)	Overall (N = 56) n (%)
Number of subjects with at least 1 TEAE	0	0	3 (37.5)	3 (37.5)	1 (12.5)	1 (12.5)	0	8 (14.3)
Number of TEAEs	0	0	4	3	4	4	0	15
Gastrointestinal disorders	**0**	**0**	**1 (12.5)**	**2 (25.0)**	**0**	**1 (12.5)**	**0**	**4 (7.1)**
Abdominal pain	0	0	0	0	0	1 (12.5)	0	1 (1.8)
Diarrhoea	0	0	1 (12.5)	0	0	1 (12.5)	0	2 (3.6)
Nausea	0	0	0	0	0	1 (12.5)	0	1 (1.8)
Paraesthesia oral	0	0	0	2 (25.0)	0	0	0	2 (3.6)
General disorders and administration site conditions	**0**	**0**	**0**	**1 (12.5)**	**0**	**0**	**0**	**1 (1.8)**
Infusion site pain	0	0	0	1 (12.5)	0	0	0	1 (1.8)
Injury, poisoning, and procedural complications	**0**	**0**	**0**	**0**	**1 (12.5)**	**0**	**0**	**1 (1.8)**
Infusion-related reaction	0	0	0	0	1 (12.5)	0	0	1 (1.8)
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**0**	**1 (12.5)**	**0**	**0**	**1 (1.8)**
Muscle tightness	0	0	0	0	1 (12.5)	0	0	1 (1.8)
Nervous system disorders	**0**	**0**	**2 (25.0)**	**0**	**0**	**1 (12.5)**	**0**	**3 (5.4)**
Dizziness	0	0	0	0	0	1 (12.5)	0	1 (1.8)
Headache	0	0	2 (25.0)	0	0	0	0	2 (3.6)
Psychiatric disorders	**0**	**0**	**0**	**0**	**1 (12.5)**	**0**	**0**	**1 (1.8)**
Anxiety	0	0	0	0	1 (12.5)	0	0	1 (1.8)

Study ML-ORI-102

In this study 52 subjects with ABSSSI received a 3-hour IV infusion of the currently approved oritavancin formulation (1200 mg diluted in 1000 ml of D5W) and 50 ABSSSI patients received a 1-hour IV Infusion of the new oritavancin formulation (1200 mg diluted in 250 ml of NS; for description of the study refer to section 3.3.1.1).

Overall, 31 subjects (59.6%) in the currently approved formulation group and 24 subjects (48.0%) in the new formulation group reported at least 1 TEAE. Of subjects with at least 1 TEAE, 20 (38.5%) in the oritavancin 400 mg formulation group, and 11 (22.0%) in the new formulation group experienced TEAEs that were considered related to study drug. There were no deaths in the study. While the majority of TEAEs in either group were mild or moderate, 1 subject (1.9%) in the 400 mg formulation group and 2 subjects (4%) in the new formulation group experienced TEAEs that were serious: 1 subject in the currently approved formulation group were assessed with cellulitis and 2 subjects in the new formulation group were assessed with cellulitis or pyelonephritis. One subject in the 400 mg formulation group discontinued from study drug due to a related TEAE of hypersensitivity (that was not considered an SAE).

Table 6: Overall summary of treatment-emergent adverse events (safety analysis); study ML- ORI-102

	Oritavancin 400 mg formulation (3-hour IV) (N = 52) n (%)	Oritavancin NF (1-hour IV) (N = 50) n (%)
Subjects with at least 1 TEAE	31 (59.6)	24 (48.0)
Subjects with a related TEAE	20 (38.5)	11 (22.0)
Subjects with a severe or higher TEAE	3 (5.8)	1 (2.0)
Subjects with a serious TEAE	1 (1.9)	2 (4.0)
Subjects with a related serious TEAE	0 (0.0)	0 (0.0)
Subjects with a TEAE leading to study drug discontinuation	1 (1.9)	0 (0.0)
Subjects with a TEAE leading to study drug interruption	3 (5.8)	2 (4.0)
Subjects with a TEAE of Special Interest	2 (3.8)	2 (4.0)

Abbreviations: IV = intravenous; TEAE = treatment-emergent adverse event.
Source: ML-ORI-102 CSR Table 14.3.2.1

Overall, TEAes reported by more than 1 subject and with a reasonable possibility of being related to study drug were diarrhoea, nausea, hypersensitivity, pruritus and pruritus generalised (Table 7).

In summary, skin and subcutaneous tissue disorders TEAEs were the most frequent TEAEs by SOC, were generally related, and occurred more frequently in the oritavancin 400 mg formulation group than the oritavancin new formulation group. Overall, pruritus events (pruritus and pruritus generalised) were nearly twice as frequent in the oritavancin 400 mg formulation group (19.2%, 10 of 52 subjects) compared with the oritavancin new formulation group (10%, 5 of 50 subjects). The remaining events in this SOC, urticaria and red man syndrome, were uncommon.

Table 7: Summary of related treatment-emergent adverse events by system organ class and preferred term (safety analysis set); study ML-ORI-102

System Organ Class Preferred Term	Current Approved (3-hour IV) (N = 52)	New (1-hour IV) (N = 50)
Number of subjects with at least 1 TEAE, n (%)	20 (38.5)	11 (22.0)
Gastrointestinal disorders, n (%)	**5 (9.6)**	**3 (6.0)**
Diarrhoea	3 (5.8)	3 (6.0)
Nausea	2 (3.8)	0 (0.0)
Vomiting	1 (1.9)	0 (0.0)
General disorders and administration site conditions	**2 (3.8)**	**2 (4.0)**
Infusion site extravasation	1 (1.9)	0 (0.0)
Infusion site pain	0 (0.0)	1 (2.0)
Infusion site swelling	1 (1.9)	0 (0.0)
Oedema peripheral	0 (0.0)	1 (2.0)
Immune system disorders	**2 (3.8)**	**1 (2.0)**
Hypersensitivity	2 (3.8)	1 (2.0)
Infections and infestations	**1 (1.9)**	**0 (0.0)**
Vulvovaginal mycotic infection	1 (1.9)	0 (0.0)
Investigations	**0 (0.0)**	**1 (2.0)**
Heart rate increased	0 (0.0)	1 (2.0)
Skin and subcutaneous tissue disorders	**11 (21.2)**	**6 (12.0)**
Pruritus	7 (13.5)	2 (4.0)
Pruritus generalized	3 (5.8)	3 (6.0)
Red man syndrome	0 (0.0)	1 (2.0)
Urticaria	1 (1.9)	0 (0.0)

Abbreviations: IV = intravenous; TEAE = treatment-emergent adverse event.
Source: Table 14.3.2.5

Adverse Events of Special Interest

- Hypersensitivity

In study ML-ORI-102, a similar percentage of subjects in the currently approved formulation group (3.8%) and new formulation group (4%) had AESIs. The AESIs were limited to hypersensitivity/infused related reactions (IRR).

For the MDCO-ORI-15-01 clinical study, there were no reported hypersensitivity AEs.

- Renal Impairment

Due to the presence of the excipient HPβCD in the new oritavancin formulation, the MAH evaluated AEs and laboratory investigations following study completion for any evidence of post-exposure renal adverse effects. Review of all AEs, related and unrelated, showed no TEAEs of renal impairment, renal failure nor similar events.

2.6.7. Discussion on clinical safety

The safety of the currently approved formulation has been well characterised in the oritavancin 400 mg formulation development program as well as in post-marketing surveillance since the oritavancin 400 mg formulation has been approved in the EU in 2015. The applied 1200 mg oritavancin formulation was developed to deliver the same dose as the currently approved 400 mg oritavancin formulation and to be administered for the same indication. However, tolerability of the faster infusion time and the excipient HPβCD which is renally eliminated are particular important for the new formulation.

Reduced infusion time

Comparison of C_{max} values from ABSSSI patients in study ML-ORI-102 and SOLO I & II showed similar values. In study ML-ORI-102, mean C_{max} (min, max) was 112 (25, 193) µg/ml and 148 (14.1, 265) µg/ml for the currently approved and new formulation, respectively, reflecting the expected increase in C_{max} for the shorter infusion time of the new formulation. In the Phase 3 studies, mean C_{max} (min, max) of the currently approved formulation was 138 (11.1, 319) µg/ml. Hence, the observed C_{max} distribution following administration of the new formulation lies within the PopPK-model derived C_{max} distribution of the currently approved formulation and a safety concern is not posed based on the C_{max} values of the new formulation alone.

Based on the results of study MDCO-ORI-15-01 in healthy volunteers, there was no evidence of an increase or change in TEAEs with a decrease in infusion time with the new formulation (Cohorts 2-5). However, the number of treated subjects is very limited (8 per Cohort) and limited to healthy subjects since different infusion times with the new formulation were not studied in ABSSSI patients.

Excipient HPβCD

The new formulation contains 2400 mg of HPβCD/vial which is a widely used modified cyclodextrin and a well characterised excipient used in other approved drugs. Safety data from studies ML-OR-102 and MDCO-ORI-15-01 did not reveal any TEAEs of renal impairment or renal failure. Sections 4.2 und 4.4 of the SmPC have been updated to include information on HPβCD.

Since there were no new safety signals with the 1200 mg oritavancin formulation, the safety information for oritavancin 400 mg formulation is anticipated to form the basis of safety information for oritavancin new package labelling which is generally considered acceptable. However, it must be kept in mind that safety data for the new formulation are very limited and based on 52 ABSSSI patients and 40 healthy volunteers included in studies ML-ORI-102 and MDCO-ORI-15-01.

2.6.8. Conclusions on clinical safety

Overall, the oritavancin new formulation with the shorter infusion time and a new excipient seems to have a comparable safety profile to the 400 mg approved formulation. Based on the submitted data and consistency of results across studies, there is no evidence of an increase or change in TEAEs with decrease of infusion time or based on the presence of HPβCD.

2.7. Risk Management Plan

The new RMP version (4.0) is being submitted as a part of line extension application. The RMP has been updated to include information on oritavancin new formulation: vial containing 1200 mg oritavancin powder for concentrate for solution for infusion. There is no change to the list of safety concerns.

The following changes were introduced:

- Part I has been updated to include the oritavancin NF;

- Part II Module SII has been updated to include in vivo studies conducted to support the safety of oritavancin NF and nonclinical safety studies with HPβCD described in published literature;

- Part II Module SV, SVII have been updated to include post-marketing exposure and safety data on oritavancin up to the Data Lock Point of this report;

- Part VI has been updated accordingly.

The invented name "Orbactiv" has been replaced with the new brand name "Tenkasi" throughout the document.

The other changes are of minor nature.

The RMP Part III-VI is acceptable.

2.7.1. Safety concerns

2.7.1.1. Summary of safety concerns

No change to the safety concerns list has been proposed.

This RMP version includes information on oritavancin new formulation: vial containing 1200 mg oritavancin powder for concentrate for solution for infusion. Oritavancin NF with its shorter infusion time, has a comparable safety profile to that of oritavancin 400 mg of powder for concentrate for solution for infusion. Since there were no new safety findings with the oritavancin NF, no change to the safety concerns list has been proposed.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity
Important potential risks	Pseudomembranous colitis / *Clostridium difficile*-associated diarrhoea (CDAD) Osteomyelitis
Missing information	None

2.7.1.2. Discussion on safety specification

Cyclodextrins [e.g. HPβCD and SBECD (sulfobutylether-β-cyclodextrin, also called betadex sulfobutyl ether sodium)] are used as excipients also in other authorised drugs for intravenous application including the anti-infectives itraconazole (HPβCD as excipient), delafloxacin (SBECD as excipient) and remdesivir (SBECD as excipient). Considering that cyclodextrins are renally excreted, in patients with moderate to severe renal dysfunction accumulation of cyclodextrin may occur. The product information of the above-mentioned drugs reflects this information. Renal damage secondary to SBECD accumulation in patients with severe renal impairment [IV formulation] is an important potential risk included in the list of safety concerns of the RMP for delafloxacin. Safety in patients with severe renal impairment is a safety concern listed as missing information in the RMP for remdesivir, where it is stated that, *the excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function. The safety of betadex sulfobutyl ether sodium in COVID-19*

patients with severe renal impairment is unknown; to further characterize this safety concern, additional pharmacovigilance activities are in place.

In the response, the MAH has provided an explanation concerning the presence of HPβCD in the new formulation. No new risk related to the presence of HPβCD has been identified at present. Taking also into consideration the information proposed to be included in sections 4.2 and 4.4. it is considered acceptable. The MAH proposed to analyse safety information related to the new formulation in future PSURs. No RMP update is considered necessary at present.

2.7.1.3. Conclusions on the safety specification

Safety Specification as per RMP version 4.0 are considered acceptable (no changes in the list of Safety Concerns).

2.7.2. Pharmacovigilance plan

The pharmacovigilance plan includes routine pharmacovigilance activities.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for oritavancin immunological (hypersensitivity) adverse events (Important Identified Risk), for oritavancin pseudomembranous colitis / CDAD adverse events (Important Potential Risks) and for oritavancin osteomyelitis adverse events (Important Potential Risk):

The aim of these questionnaires is to obtain structured and detailed information on reports of these adverse reactions. The forms are provided in Annex 4 of this RMP.

- Other forms of routine pharmacovigilance activities:

  Not applicable.

A review of the safety concerns is planned to be performed at each PSUR elaboration.

2.7.2.1. Summary of planned additional PhV activities from RMP

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 3 - Required additional pharmacovigilance activities				
None	Not applicable	Not applicable	Not applicable	Not applicable

2.7.2.2. Overall conclusions on the PhV Plan

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.3. Plans for post-authorisation efficacy studies

Not applicable.

There are no ongoing or planned imposed post-authorisation efficacy studies concerning oritavancin containing products.

2.7.4. Risk minimisation measures

2.7.4.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk: Hypersensitivity	Routine risk communication:

	- SmPC section 4.3 Contraindications - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects The PL of the concerned products is in line with the information contained in the SmPC previously described. Such information is given in the following sections of the PL: - PL Section 2 What you need to know before you take – You must not be given – Warnings and precautions - PL Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: - Contraindication in patients with hypersensitivity to the active substance or to any of the excipients in SmPC section 4.3. - Recommendations to discontinue oritavancin and to institute appropriate supportive care if acute hypersensitivity reaction occurs during oritavancin infusion are reported in in SmPC section 4.4 . 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. Serious hypersensitivity reactions, including anaphylactic reactions and anaphylactic shock have been reported with the use of oritavancin. - The most commonly reported adverse reactions (≥5%) were: hypersensitivity reactions, infusion site reactions. ADRs related to hypersensitivity are reported in SmPC section 4.8. No other routine risk minimisation measures were included beyond the Product Information. Legal status: prescription only medicine
Important Potential Risks: Pseudomembranous colitis / *Clostridium difficile*-associated diarrhoea (CDAD)	Routine risk communication: - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects The PL of the concerned products is in line with the information contained in the SmPC previously described. Such information is given in the following sections of the PL: - PL Section 2 What you need to know before you take – Warnings and precautions - PL Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: - Recommendations to consider the diagnosis of antibacterial-associated colitis and pseudomembranous colitis in patients who present with diarrhoea subsequent to the administration of oritavancin are reported in SmPC section 4.4. In such a circumstance, the use of supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered.

	- Diarrhoea is included as a common ADR in SmPC section 4.8. No other routine risk minimisation measures were included beyond the Product Information. Legal status: prescription only medicine
Important Potential Risks: Osteomyelitis	Routine risk communication: - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects The PL of the concerned products is in line with the information contained in the SmPC previously described. Such information is given in the following sections of the PL: - PL Section 2 What you need to know before you take – Warnings and precautions - PL Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: - Recommendations to monitor patients with signs and symptoms of osteomyelitis after administration of oritavancin are reported in SmPC section 4.4. If osteomyelitis is suspected or diagnosed, appropriate alternative antibacterial therapy should be instituted. - The most common reported reasons for discontinuation were cellulitis (0.4%) and osteomyelitis (0.3%). Osteomyelitis is reported as an uncommon ADR in SmPC section 4.8. No other routine risk minimisation measures were included beyond the Product Information. Legal status: prescription only medicine

2.7.4.2. Additional risk minimisation measures

None.

2.7.4.3. Overall conclusion on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.7.5. Conclusion

The CHMP considered that the risk management plan version 4 is acceptable and approved with this procedure.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

Not applicable – Module 1.8.1 has not been submitted.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports 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.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reason:

- the information given in the PI of the new formulation only slightly differs from the approved PI of the 400 mg formulation.

3. Benefit-Risk Balance

The new 1200 mg oritavancin formulation was developed to simplify the preparation for solution for infusion but to deliver the same dose as the currently approved 400 mg oritavancin formulation and to be administered for the same indication.

Apart from the single-vial presentation, the new formulation has the advantage that the active substance can be diluted to a smaller volume (250 ml instead of 1000 ml) with either NS or D5W and infused over a shorter period of time (1 hour instead of 3 hours).

Based on the results of study ML-ORI-102 oritavancin exposure in patients with ABSSSI is comparable between the two formulations indicating that efficacy data of the currently approved formulation can be applied to the new formulation. Increased C_{max} values due to shorter infusion time are still comparable to PopPK-data derived from the Phase 3 studies conducted with the currently approved formulation and thus do not pose a safety concern.

The safety profile of the currently approved 400 mg formulation has been well characterised during development and post-marketing. Safety data of the new formulations are limited and based on 52 ABSSSI patients and 40 healthy volunteers included in the two Phase 1 studies ML-ORI-102 and MDCO-ORI-15-01. However, TEAS were comparable between treatment groups despite the reduced infusion time and presence of the excipient HPβCD and information on HPβCD were included in sections 4.2 and 4.4 of the SmPC.

Benefit-Risk is positive,sche with a shelf-life of 4 years.

3.1. Conclusions

The overall benefit /risk balance of Tenkasi 1200 mg solution for infusion is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety, the CHMP considers by consensus that the benefit-risk balance of Tenkasi 1200 mg, is favourable in the following indication:

treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Tenkasi subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports 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.

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.