▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

VIBATIV 750 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 750 mg telavancin (as hydrochloride).

After reconstitution, each ml contains 15 mg of telavancin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion
A white to pale pink, whole or fragmented cake

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VIBATIV is indicated for the treatment of adults with nosocomial pneumonia (NP) including ventilator associated pneumonia, known or suspected to be caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

VIBATIV should be used only in situations where it is known or suspected that other alternatives are not suitable (see sections 4.3, 4.4, 4.8 and 5.1).

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

4.2 Posology and method of administration

Posology

Adults
The recommended dosage regimen is 10 mg/kg, once every 24 hours, for 7 to 21 days.

Special populations

Elderly patients
Elderly patients should receive a telavancin dose in accordance with their bodyweight and renal function (see sections 4.3 and 5.2).

Renal impairment
Patients with renal impairment should receive an initial dose according to calculated or measured creatinine clearance as presented in the table below. During treatment dose adjustments according to the table should be made based on calculated or measured creatinine clearance in patients with clinically relevant changes in renal function.

Creatinine clearance* (ml/min)	Dosage regimen

>50	10 mg/kg every 24 hours
30-50	7.5 mg/kg every 24 hours

*As calculated using the Cockcroft-Gault formula

The use in patients with acute renal failure or creatinine clearance (CrCl) <30 ml/min including patients undergoing haemodialysis is contraindicated (see section 4.3).

Hepatic impairment
Mild to moderate degrees of hepatic impairment (Child-Pugh class B) (see section 5.2) did not result in a relevant change in pharmacokinetics of telavancin. Therefore, no dose adjustment is necessary when administering telavancin to subjects with mild or moderate degrees of hepatic impairment. No data are available in subjects with severe hepatic impairment (Child-Pugh class C). Therefore, caution should be exercised if telavancin is given to subjects with severe hepatic impairment.

Obese patients
Obese patients (defined as those with BMI > 30 kg/m^2) should receive telavancin at the reduced dose of 7.5 mg/kg once every 24 hours (see section 5.2).

Paediatric patients
The safety and efficacy of VIBATIV in children and adolescents aged below 18 years have not yet been established. No data are available.

Method of administration

For intravenous use.

VIBATIV must be reconstituted and then further diluted prior to administration by intravenous infusion through a dedicated line or through a Y-site over a 60 minute period. Bolus injections must not be administered. For instructions on reconstitution and dilution, see section 6.6.

4.3 Contraindications

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

Patients with severe renal impairment, i.e. creatinine clearance (CrCl) <30 ml/min, including patients undergoing haemodialysis (see section 4.4).

Acute renal failure (see section 4.4).

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Renal impairment

In the clinical studies, patients with pre existing acute renal failure receiving telavancin had an increased risk of mortality. All-cause mortality was 32/73 (44%) in the telavancin group and 16/64 (25%) in the vancomycin group, whereas in patients without acute renal failure at baseline it was 118/678 (17%) and 124/688 (18%), respectively. Therefore, the use of telavancin in patients with pre-existing acute renal failure and in patients with severe renal impairment is contraindicated (see section 4.3).

Renal adverse reactions

In the pooled clinical studies (NP and complicated skin and soft tissue infection (cSSTI)), renal adverse reactions were reported more frequently in patients receiving telavancin compared with vancomycin (3.8% vs. 2.2%, respectively). Renal function (serum creatinine and urinary output for

oliguria/anuria) should be monitored daily for at least the first 3 to 5 days of therapy and every 48 to 72 hours thereafter in all patients receiving telavancin. Initial dose and dosage adjustments during treatment should be made based on calculated or measured creatinine clearance according to the dosing regimen in section 4.2. If renal function markedly decreases during treatment, the benefit of continuing telavancin should be assessed.

Other factors that may increase the risk of nephrotoxicity

Caution should be used when prescribing VIBATIV to patients receiving concomitant nephrotoxic medicines, those with pre existing renal disease or with co-morbidity known to predispose to kidney dysfunction (e.g. diabetes mellitus, congestive heart failure, hypertension).

Infusion related reactions

Rapid intravenous infusions of antimicrobial agents of the class of glycopeptides have been associated with red man syndrome-like reactions, including flushing of the upper body, urticaria, pruritus or rash (see section 4.8). Stopping or slowing the infusion may result in cessation of these reactions. Infusion related reactions can be limited if the daily dose is infused over a 1 hour period.

Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, have been reported with telavancin, and may be life-threatening. If an allergic reaction to telavancin occurs, discontinue treatment and institute appropriate therapy.

Cross hypersensitivity reactions, including anaphylaxis, have been reported in patients with a history of vancomycin allergy. Caution should be exercised when prescribing telavancin to patients with a prior history of hypersensitivity reaction to vancomycin. If an allergic reaction to telavancin occurs, discontinue treatment and institute appropriate therapy.

QTc prolongation

A clinical QTc study with telavancin doses of 7.5 and 15 mg/kg versus vehicle and an active comparator (400 mg moxifloxacin) showed that once daily dosing for 3 days resulted in a mean vehicle corrected increase in QTcF by 4.1 and 4.5 millisecond, respectively, compared to a 9.2 millisecond increase observed with the comparator.

Caution is warranted when using telavancin to treat patients taking medicinal products known to prolong the QT interval. In addition, caution is warranted when using telavancin to treat patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy. Patients with these conditions were not included in clinical trials of telavancin.

Ototoxicity

As with other glycopeptides, ototoxicity (deafness and tinnitus) has been reported in patients treated with telavancin (see section 4.8). Patients who develop signs and symptoms of impaired hearing or disorders of the inner ear during treatment with telavancin should be carefully evaluated and monitored (see section 4.8). Patients receiving telavancin in conjunction with or sequentially with other medicinal products with known ototoxic potential should be carefully monitored and the benefit of telavancin evaluated if hearing deteriorates.

Superinfection

The use of antibiotics may promote the overgrowth of non-susceptible micro-organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Antibiotic-associated colitis and pseudomembranous colitis

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all antibacterial agents, including telavancin (see section 4.8), and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or shortly following treatment.

Concomitant antibiotic coverage

Telavancin is active against Gram-positive bacteria only (see section 5.1 for information on the antimicrobial spectrum). In mixed infections where Gram-negative and/or certain types of anaerobic bacteria are suspected, VIBATIV should be co-administered with appropriate antibacterial agent(s).

Specific patient groups

The nosocomial pneumonia (NP) studies excluded known or suspected pulmonary disease like granulomatous diseases, lung cancer, or other malignancy metastatic to the lungs; cystic fibrosis or active tuberculosis; *Legionella pneumophila* pneumonia; meningitis, endocarditis, or osteomyelitis; refractory shock defined as supine systolic blood pressure <90 mm Hg for >2 hours with evidence of hypoperfusion or requirement for high-dose sympathomimetic agents. Also patients with baseline QTc >500 msec, congenital long QT syndrome, uncompensated heart failure, or abnormal K^+ or Mg^{2+} blood levels that could not be corrected, severely neutropenic (absolute neutrophil count <500/mm^3) or anticipated to develop severe neutropenia due to prior or planned chemotherapy, or who had HIV with CD4 count <100/mm^3 during the last 6 months were excluded.

4.5 Interaction with other medicinal products and other forms of interaction

In studies in healthy subjects, the pharmacokinetics of telavancin were not significantly altered by simultaneous administration of aztreonam or piperacillin-tazobactam. Also, the pharmacokinetics of aztreonam or piperacillin tazobactam were not altered by telavancin. Based on their pharmacokinetic properties, no interaction is expected with other beta-lactams, clindamycin, metronidazole, or fluoroquinolones.

It was demonstrated in a clinical study with intravenous midazolam that multiple doses of telavancin had no effect on the pharmacokinetics of midazolam, which is a sensitive substrate for CYP3A4. *In vitro* experiments indicate that telavancin will not affect the clearance of medicinal products metabolised by CYP isoforms 1A2, 2C9, 2C19 and 2D6. Since telavancin is primarily excreted unchanged by renal clearance and multiple CYP enzymes are able to metabolise telavancin, no relevant interactions are expected with inhibitors or inducers of the CYP450 system.

Although telavancin does not interfere with coagulation, it interfered with certain tests used to monitor coagulation (see below), when tests are conducted using samples drawn between 0 to 18 hours after telavancin administration to patients being treated once every 24 hours. Blood samples for coagulation tests should be collected as closely as possible prior to a patient's next dose of telavancin or consideration given to using a test unaffected by telavancin.

Coagulation tests affected by telavancin	Coagulation tests unaffected by telavancin
International normalised ratio	Whole blood (Lee-White) clotting time
Activated partial thromboplastin time	Ex vivo platelet aggregation
Activated clotting time	Chromogenic factor Xa assay
Coagulation based factor Xa tests	Functional (chromogenic) factor X assay
	Bleeding time
	D-dimer
	Fibrin degradation products

No evidence of increased bleeding risk has been observed in clinical trials with telavancin. Telavancin has no effect on platelet aggregation. Furthermore, no evidence of hypercoagulability has been seen, as healthy subjects receiving telavancin have normal levels of D-dimer and fibrin degradation products.

Telavancin interferes with urine qualitative dipstick protein assays, as well as quantitative dye methods (e.g. pyrogallol red molybdate). Microalbumin assays based on immunoassay utilizing nephelometric (turbidity) detection are not affected and can be used to monitor urinary protein excretion during telavancin treatment. For routine monitoring of renal function it is recommended to use serum creatinine concentration or estimated creatinine clearance.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of VIBATIV is contraindicated during pregnancy (see section 4.3).
There is no human experience with telavancin. Studies in animals have shown reproductive toxicity (see section 5.3).

The pregnancy status of women of childbearing potential has to be established prior to dosing with telavancin. Women of childbearing potential have to use effective contraception during treatment.

Breastfeeding

It is unknown whether telavancin is excreted in human breast milk. The excretion of telavancin in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with telavancin should be made taking into account the benefit of breastfeeding to the child and the benefit of telavancin therapy to the woman.

Fertility

Telavancin has been shown to affect sperm quantity and quality of male rats (see section 5.3) although no effect on fertility, mating, or early embryogenesis has been reported. The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

Dizziness, somnolence, confusion and blurred vision may occur and VIBATIV may have an influence on the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In phase 3 clinical trials involving 1680 patients (751 and 929, NP and cSSTI, respectively) who received telavancin at a daily dose of 10 mg/kg, adverse reactions were reported in 47.3% of patients. Treatment was discontinued due to adverse reactions in 5.0% of patients who received telavancin.

The most commonly reported related adverse reactions (occurring in >1% of patients) were: fungal infection, insomnia, dysgeusia, headache, dizziness, nausea, constipation, diarrhoea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, pruritus, rash, renal failure acute, blood creatinine increased, urine abnormality (foamy urine), fatigue and chills.

Tabulated list of adverse reactions

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not

known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations	
Common:	fungal infection
Uncommon:	clostridium colitis, urinary tract infection
Blood and lymphatic system disorders	
Uncommon:	anaemia, leukopenia, thrombocythaemia, thrombocytopenia, eosinophil count increased, neutrophil count increased
Immune system disorders	
Uncommon:	hypersensitivity
Not known*	anaphylaxis
Metabolism and nutrition disorders	
Uncommon:	decreased appetite, hyperglycaemia, hyperkalaemia, hypoglycaemia, hypokalaemia, hypomagnesaemia
Psychiatric disorders	
Common:	insomnia
Uncommon:	agitation, anxiety, confusional state, depression
Nervous system disorders	
Very common:	dysgeusia
Common:	headache, dizziness
Uncommon:	ageusia, migraine, paraesthesia, parosmia, somnolence, tremor
Eye disorders	
Uncommon:	eye irritation, blurred vision
Ear and labyrinth disorders	
Uncommon:	tinnitus
Rare:	deafness
Cardiac disorders	
Uncommon:	angina pectoris, atrial fibrillation, bradycardia, cardiac failure congestive, electrocardiogram QT corrected interval prolonged, palpitations, sinus tachycardia, supraventricular extrasystoles, ventricular extrasystoles
Vascular disorders	
Uncommon:	flushing, hypertension, hypotension, phlebitis
Respiratory, thoracic and mediastinal disorders	
Uncommon:	dyspnoea, hiccups, nasal congestion, pharyngolaryngeal pain
Gastrointestinal disorders	
Very common:	nausea
Common:	constipation, diarrhoea, vomiting
Uncommon:	abdominal pain, dry mouth, dyspepsia, flatulence, hypoaesthesia oral
Hepatobiliary disorders	
Common:	alanine aminotransferase increased, aspartate aminotransferase increased
Uncommon:	hepatitis

Skin and subcutaneous tissue disorders

Common:	pruritus, rash
Uncommon:	erythema, face oedema, hyperhidrosis, urticaria

Musculoskeletal and connective tissue disorders

Uncommon:	arthralgia, back pain, muscle cramp, myalgia

Renal and urinary disorders

Common:	renal failure acute, blood creatinine increased, foamy urine (lower level term)
Uncommon:	blood urea increased, dysuria, haematuria, microalbuminuria, oliguria, pollakiuria, renal impairment, urine odour abnormal

General disorders and administration site conditions

Common:	fatigue, chills
Uncommon:	asthenia, infusion site reactions, malaise, non-cardiac chest pain, peripheral oedema, pain, pyrexia, Red Man syndrome

Investigations

Uncommon:	international normalised ratio increased

* Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

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:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

In healthy volunteers who received a dose of 15 mg/kg, a higher incidence of adverse reactions to telavancin was seen: dysgeusia, nausea, vomiting, injection site erythema, headache, macular rash, and red man syndrome.

In the event of overdose, telavancin should be discontinued and supportive care is advised with maintenance of glomerular filtration and careful monitoring of renal function. Following

administration of a single dose of telavancin 7.5 mg/kg to subjects with end-stage renal disease, approximately 5.9% of the administered dose of telavancin was recovered in the dialysate following 4 hours of haemodialysis. However, no information is available on the use of haemodialysis to treat an overdose.

The clearance of telavancin by continuous venovenous haemofiltration (CVVH) was evaluated in an *in vitro* study. Telavancin was cleared by CVVH and the clearance of telavancin increased with increasing ultrafiltration rate. However, the clearance of telavancin by CVVH has not been evaluated in a clinical study; thus, the clinical significance of this finding and use of CVVH to treat an overdose are unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, glycopeptide antibacterials, ATC code: J01XA03

Mechanism of action

Telavancin exerts concentration-dependent bactericidal activity against susceptible Gram-positive bacteria. Telavancin inhibits cell wall biosynthesis by binding to late-stage peptidoglycan precursors, including lipid II, which prevents polymerisation of the precursor into peptidoglycan and subsequent cross-linking events. Telavancin also binds to bacterial membranes and causes depolarisation of membrane potential and an increase in membrane permeability that results in inhibition of protein, RNA, and lipid synthesis.

Mechanism of resistance

S. aureus that exhibit high level resistance to glycopeptide antibacterial agents (GRSA) are not susceptible to telavancin. There is no known cross-resistance between telavancin and other non-glycopeptide classes of antibiotics.

Breakpoints

The minimum inhibitory concentration (MIC) breakpoints are as follows:

Pathogen	**MIC (µg/ml)**
S. aureus (including methicillin-resistant strains)	≤0.12

Microbiological susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Clinical efficacy and safety
Telavancin demonstrated efficacy against MSSA and MRSA in two randomised controlled studies in patients with nosocomial pneumonia, including ventilator-associated pneumonia, involving 751 patients who received telavancin. Despite *in vitro* susceptibility, there are insufficient clinical data to assess the potential for efficacy of telavancin in infections due to hGISA/GISA.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with telavancin in one or more subsets of the paediatric population in nosocomial pneumonia. See 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Telavancin exhibited linear pharmacokinetics at doses up to 15 mg/kg administered as a daily 60 minute intravenous infusion for 7 days in healthy volunteers. The mean (SD) maximum telavancin concentration (C_{max}) amounts to 108 (26) µg/ml at steady state at a once daily dose of 10 mg/kg infused over a period of 1 h (t_{max}) and then falls to a trough value of 8.55 (2.84) µg/ml (C_{24h}). Mean (SD) AUC_{0-24} amounts to 780 (125) µg.h/ml. Telavancin has a small volume of distribution. At a dose of 10 mg/kg, mean V_{ss} averaged between 133 (SD 24) ml/kg after multiple dosing, corresponding to a value of approximately 10 l for a 75 kg person. This data indicate that telavancin is not extensively distributed. Telavancin is a low clearance active substance with a mean (SD) CL of 13.1 (2.0) ml/hr/kg in subjects with normal renal function, corresponding to a total CL of approximately 1 l/hr in a 75 kg subject. In combination with the small V_{ss}, this results in a $t_{1/2}$ of about 8 h.

Distribution

The apparent distribution volume of telavancin at steady-state in healthy adult subjects was approximately 133 ml/kg.

Human plasma protein binding is approximately 90%, primarily to serum albumin.

At a dose of 10 mg/kg for 3 consecutive days to healthy volunteers subjected to bronchoalveolar lavage, the concentration ratio in pulmonary epithelial lining fluid/plasma ranged from 0.050 and 0.121 over a period of 4 to 24 hours after start of infusion. Higher concentrations were observed in alveolar macrophages with ratios varying between 0.360 (at 4 h) and 6.67 (at 24 h). *In vitro* studies showed that telavancin retained full activity in the presence of pulmonary surfactant.

Biotransformation

In vitro studies have shown that CYP1A1, 1A2, 2B6, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5 and 4F12 are able to metabolise telavancin, resulting in hydroxylation at the 7, 8 and 9 position of the 2-(decylamino) ethyl side chain of telavancin.

In a mass balance study in male subjects using radiolabeled telavancin, 3 hydroxylated metabolites were identified with the predominant metabolite (THRX-651540) accounting for <10% of the radioactivity in urine and <2% of the radioactivity in plasma.

In healthy young adults, three hydroxylated metabolites were identified after infusion of telavancin. The AUC of the predominant metabolite accounted for approximately 2-3% of AUC of telavancin.

Elimination

Renal excretion is the major route of elimination for telavancin in humans. In healthy young adults, after infusion of radiolabeled telavancin, approximately 76% of the administered dose was recovered from urine and less than 1% of the dose was recovered from faeces (collected for up to 9 days), based on total radioactivity. Telavancin is mainly excreted unchanged accounting for approximately 82% of the total amount recovered over 48 hours in urine. The elimination half-life in subjects with normal renal function is approximately 8 hours.

Because renal excretion is the primary route of elimination, dosage adjustment is necessary in patients with a creatinine clearance of 30-50 ml/min (see section 4.2).

Special populations

Elderly
No clinically significant differences in pharmacokinetics of telavancin were observed between healthy elderly and healthy young subjects. Analysis of patient population pharmacokinetic data did not show a relevant effect of age on pharmacokinetics. Therefore, no dose adjustment is needed in elderly patients except in those with creatinine clearance of 30-50 ml/min (see sections 4.2 and 4.3).

Paediatric patients
The pharmacokinetics of telavancin in patients below 18 years of age have not been established (see section 4.2).

Gender
No clinically significant gender-related differences in telavancin pharmacokinetics have been observed. Therefore, no dosage adjustment is necessary based on gender.

Renal insufficiency
Pharmacokinetic parameters (mean (SD)) following a single dose administration of 7.5 mg/kg telavancin in volunteers with varying degrees of renal function are provided below.

	Degree of Renal Impairment				
	Normal	Mild	Moderate	Severe	ESRD[a]
CrCL (ml/min)[b]	93.8 (10.8)	64.1 (9.7)	40.3 (7.0)	21.0 (6.3)	NA
C_{max} (μg/ml)	70.6 (11.2)	65.9 (2.7)	65.8 (12.1)	71.8 (7.1)	52.1 (10.1)
AUC_{inf} (μg·h/ml)	560 (93)	633 (101)	721 (200)	1220 (120)	1010 (341)
$t_{1/2}$ (h)	6.90 (0.60)	9.6 (2.9)	10.6 (2.4)	14.5 (1.3)	11.8 (2.8)
CL (ml/h/kg)	13.7 (2.1)	12.1 (1.9)	11.1 (3.3)	6.18 (0.63)	8.18 (2.65)

[a] ESRD= End-stage renal disease maintained on haemodialysis
[b] Baseline mean creatinine clearance as calculated by Cockcroft-Gault equation

The effect of renal impairment on the pharmacokinetics of telavancin has been evaluated in 2 clinical pharmacology studies in healthy subjects with normal renal function and subjects with mild to severe renal impairment. Both studies consistently showed that the area under the curve (AUC) of telavancin, but not the maximum plasma concentration (C_{max}) increases with decreasing renal function. Changes in AUC only become clinically relevant in patients with moderate and severe renal impairment. Therefore, the same dose of 10 mg/kg/24 hr can be used in patients with normal renal function or mild renal impairment. To ensure a comparable exposure in patients with moderate renal impairment, the dose should be lowered to 7.5 mg/kg/24 hr.

Recommendations for dose adjustment can be found in section 4.2.

Hepatic impairment
Following administration of a single 10 mg/kg dose of telavancin, the pharmacokinetics of telavancin in subjects with moderate hepatic impairment (Child-Pugh class B) were similar to that observed in subjects with normal hepatic function. No adjustment of dosage is required for patients with mild to moderate degrees of hepatic impairment (see section 4.2). The pharmacokinetics of telavancin have not been evaluated in severe hepatic impairment (Child-Pugh class C).

Obese patients
Body mass index (BMI) at baseline was found to influence telavancin pharmacokinetics in the population pharmacokinetic analysis in healthy (without infection) adult subjects. Exposure to telavancin increases with increase in BMI; for each 10-unit increase in BMI, it is estimated that plasma exposure will increase by up to 25%. A dose adjustment should be made in obese patients with BMI > 30 kg/m^2 (see section 4.2).

5.3 Preclinical safety data

The telavancin medicinal product, which contains the excipient hydroxypropylbetadex (HP-β-CD), induced adverse effects in animal studies at plasma concentrations that were in the same range as clinical exposure levels and with possible relevance to clinical use.

The liver, kidney, macrophages and testis were identified as target organs of toxicity in animals. In the liver, treatment for 13 weeks or longer resulted in reversible degeneration/necrosis of hepatocytes accompanied by elevations in serum AST and ALT in rats and dogs.

Effects on the kidney occurred after a minimum of 4 weeks of dosing and were a combination of renal tubular injury and tubular epithelial vacuolisation. The tubular injury was characterised by degeneration and necrosis of proximal tubular cells, and was associated with increases in BUN and creatinine that reach a maximum of 2 times the control values at the highest doses. The tubular injury was reversible, but not all animals had yet reached full recovery 4 weeks after the end of treatment.

Vacuolisation of tubular epithelium was a common observation in animals treated with the telavancin medicinal product and with the vehicle (HP-β-CD). At higher doses or longer treatment durations, vacuolisation of the urothelium in the bladder also occurred. Vacuolisation was not associated with renal function impairment, but was not reversible after 4 weeks of recovery. Vacuolisation is considered to represent a cytoprotective event and is expected to reverse with the same half-life as the turnover time of the proximal tubular cells. The presence of hydroxypropylbetadex in the formulation at a ratio of 1:10 reduces the incidence and severity of the changes due to telavancin and attenuates the glycopeptides-like toxicity of telavancin.

Systemic macrophage hypertrophy and hyperplasia occurred in rats and dogs, in many organ systems that normally contain macrophages. The macrophages were shown to contain telavancin and HP-β-CD.

Genotoxicity was addressed with a standard *in vitro* and *in vivo* test battery. The studies did not provide any evidence for a genotoxic potential of telavancin.

After 13 weeks of treatment, reversible seminiferous tubular degeneration was observed in the testis of rats. In studies on fertility in male rats, decreases in sperm motility and epididymal sperm counts as well as an increase in the frequency of abnormal sperm were demonstrated after 10 weeks of intravenous administration of telavancin. Male fertility was unaffected. In a second study, 6 weeks of dosing was associated with sloughed testicular germ cells in the epididymis, indicative of testicular injury, and effects upon sperm quality and quantity were observed. Both effects were reversible following an 8 week recovery period. The potential risk for humans is unknown (see section 4.6).

In rats and dogs vacuolisation of the epididymal tubular epithelium cells was also noted, and this finding did not show reversibility after a recovery period of 4 weeks. Vacuolisation is considered to be a cytoprotective event, which is not associated with functional impairment.

In embryo-fetal development studies malformations of digits and limbs were observed in rats, rabbits and minipigs. In the rat embryo-fetal development study dilatation of lateral ventricles of the brain was observed in the high dose group. An increase in the number of stillborn pups was observed in these pre- and post-natal studies (see section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex; the ratio of telavancin to hydroxypropylbetadex is 1:10 (w/w).
Mannitol (E421)

Sodium hydroxide (for pH adjustment) (E524)
Hydrochloric acid (for pH adjustment) (E507)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf life of powder as packaged for sale: 4 years

Shelf life of reconstituted concentrate: The reconstituted concentrate should be diluted immediately after preparation.

Shelf life of diluted product: Chemical and physical in use stability of the reconstituted solution and the diluted solution in the infusion bag has been demonstrated for 24 hours under refrigeration (2-8°C).
From a microbiological point of view the product should be used immediately. If not used immediately, in use storage times are the responsibility of the user and should not be longer than 24 hours at 2-8°C.

6.4 Special precautions for storage

Powder as packed for sale

Store in a refrigerator (2–8°C). Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted or diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I clear glass vials with rubber stoppers and aluminium/plastic flip off cap.

Pack sizes:

1 vial of 50 ml with 750 mg telavancin

6.6 Special precautions for disposal and other handling

The powder must be reconstituted and the resulting concentrate must then be immediately diluted further prior to use.

For single use only.

Preparation of the reconstituted concentrate

VIBATIV 750 mg powder for concentrate for solution for infusion
The contents of the vial containing 750 mg telavancin must be reconstituted with 45 ml of either dextrose 50 mg/ml (5%) solution for injection, or water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to obtain a concentration of approximately 15 mg/ml (total volume of approximately 50 ml).

Discard the vial if the vacuum does not pull the diluent into the vial.

Aseptic technique must be used to reconstitute VIBATIV. After addition of either dextrose 50 mg/ml (5%) solution for injection, or water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection, the contents of the vial are mixed by swirling gently to facilitate reconstitution.

Reconstitution time is not more than 10 minutes for the vial containing 750 mg.
Mixing is continued until the content of the vial is completely dissolved and is free of particulate matter by visual inspection.

Appearance of reconstituted concentrate

A reconstituted concentrate of VIBATIV is a clear, colourless to pale pink solution. Foaming may occur during reconstitution but will dissipate upon standing.

Preparation of final diluted solution for infusion

Reconstituted concentrate must be further diluted prior to administration.

The following formula can be used to calculate the volume of reconstituted VIBATIV concentrate required to prepare a dose:
Telavancin dose (mg) = 10 mg/kg (or 7.5 mg/kg) x patient body weight (in kg)
Volume of reconstituted concentrate (ml) = Telavancin dose (mg)/15 (mg/ml)

For doses of 150 to 800 mg, the appropriate volume of reconstituted concentrate must be further diluted in 100 to 250 ml prior to infusion. Doses less than 150 mg or greater than 800 mg should be further diluted in a volume resulting in a final solution of 0.6 to 8 mg/ml. Appropriate infusion solutions include: dextrose 50 mg/ml (5%) solution for injection, sodium chloride 9 mg/ml (0.9%) solution for injection or lactated Ringer's solution for injection. The dilution is to be made under aseptic conditions.

The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Disposal
Discard any unused solution.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/705/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 September 2011
Date of latest renewal: 26 May 2016

10. DATE OF REVISION OF THE TEXT

26/05/2016

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