Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Teicoplanin Hikma 400mg Powder for solution for injection/infusion or oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 400 mg teicoplanin equivalent to not less than 400,000 IU.

After reconstitution, the solutions will contain 200 mg of teicoplanin in 3.0 ml and 400 mg in 3.0 ml.

Excipient(s) with known effect: 10 mg of sodium per vial

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for Injection/infusion or oral solution.
White to yellowish lyophilized powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Teicoplanin Hikma is indicated in adults and in children from birth for the parenteral treatment of the following infections (see sections 4.2, 4.4 and 5.1):

- complicated skin and soft tissue infections,
- bone and joint infections,
- hospital acquired pneumonia,
- community acquired pneumonia,
- complicated urinary tract infections,
- infective endocarditis,
- peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD),
- bacteraemia that occurs in association with any of the indications listed above.

Teicoplanin Hikma is also indicated as an alternative oral treatment for *Clostridioides difficile* infection-associated diarrhoea and colitis.

Where appropriate, teicoplanin should be administered in combination with other antibacterial agents.

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

4.2 Posology and method of administration

Posology
The dose and duration of treatment should be adjusted according to the underlying type and severity of infection and clinical response of the patient, and patient factors such as age and renal function.

Measurement of serum concentrations
Teicoplanin trough serum concentrations should be monitored at steady state after completion of the loading dose regimen in order to ensure that a minimum trough serum concentration has been reached:

- For most Gram-positive infections, teicoplanin trough levels of at least 10 mg/L when measured by High Performance Liquid Chromatography (HPLC), or at least 15 mg/L when measured by Fluorescence Polarization Immunoassay (FPIA) method.
- For endocarditis and other severe infections, teicoplanin trough levels of 15-30 mg/L when measured by HPLC, or 30-40 mg/L when measured by FPIA method.

During maintenance treatment, teicoplanin trough serum concentrations monitoring may be performed at least once a week to ensure that these concentrations are stable.

Adults and elderly patients with normal renal function

Indications	**Loading dose**		**Maintenance dose**	
	Loading dose regimen	**Targeted trough concentrations at day 3 to 5**	**Maintenance dose**	**Targeted trough concentrations during maintenance**
• Complicated skin and soft tissue infections • Pneumonia • Complicated urinary tract infections	6 mg/kg bodyweight every 12 hours for 3 intravenous or intramuscular administrations	>15 mg/L1	6 mg/kg body weight intravenous or intramuscular once a day	>15 mg/L1 once a week
- Bone and joint infections	12 mg/kg bodyweight every 12 hours for 3 to 5 intravenous administrations	>20 mg/L1	12 mg/kg body weight intravenous or intramuscular once a day	>20 mg/L1
- Infective endocarditis	12 mg/kg bodyweight every 12 hours for 3 to 5 intravenous administrations	30-40 mg/L1	12 mg/kg body weight intravenous or intramuscular once a day	>30 mg/L1

1 Measured by FPIA
The dose is to be adjusted on bodyweight whatever the weight of the patient.

Duration of treatment
The duration of treatment should be decided based on the clinical response. For infective endocarditis a minimum of 21 days is usually considered appropriate. Treatment should not exceed 4 months.

Combination therapy
Teicoplanin has a limited spectrum of antibacterial activity (Gram positive). It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a high suspicion that the most likely pathogen(s) would be suitable for treatment with teicoplanin.

Clostridioides difficile infection-associated diarrhea and colitis
The recommended dose is 100-200 mg administered orally twice a day for 7 to 14 days.

Elderly population
No dose adjustment is required, unless there is renal impairment (see below).

Adults and elderly patients with impaired renal function

Dose adjustment is not required until the fourth day of treatment, at which time dosing should be adjusted to maintain a serum trough concentration of at least 10 mg/L when measured by HPLC, or at least 15 mg/L when measured by FPIA method. After the fourth day of treatment:

- In mild and moderate renal insufficiency (creatinine clearance 30-80 mL/min): maintenance dose should be halved, either by administering the dose every two days or by administering half of this dose once a day.
- In severe renal insufficiency (creatinine clearance less than 30 mL/min) and in haemodialysed patients: dose should be one-third the usual dose, either by administering the initial unit dose every third day or by administering one-third of this dose once a day.

Teicoplanin is not removed by haemodialysis.

Patients incontinuous ambulatory peritonea ldialysis (CAPD)
After a single intravenous loading dose of 6 mg/kg bodyweight, 20 mg/L is administered in the bag of the dialysis solution in the first week, 20 mg/L in different bags the second week and then 20 mg/L in the overnight bag in the third week.

Paediatric population
The dose recommendations are the same in adults and children above 12 years of age.

Neonates and infants up to the age of 2 months: Loading dose
One single dose of 16 mg/kg body weight, administered intravenously by infusion on the first day.
Maintenance dose
One single dose of 8 mg/kg body weight administered intravenously by infusion once a day.

Children (2 months to12 years): Loading dose
One single dose of 10 mg/kg body weight administered intravenously every 12 hours, repeated 3 times.
Maintenance dose
One single dose of 6-10 mg/kg body weight administered intravenously once a day.

Method of administration
Teicoplanin should be administered by the intravenous or intramuscular route. The intravenous injection may be administered either as a bolus over 3 to 5 minutes or as a 30-minute infusion.
Only the infusion method should be used in neonates and infants up to the age of 2 months.

For *Clostridioides difficile* infection-associated diarrhoea and colitis, the oral route is to be used.

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

4.3 Contraindications

Hypersensitivity to teicoplanin or to any of the excipients listed in section 6.

4.4 Special warnings and precautions for use

Teicoplanin should not be administered by intraventricular use.

Hypersensitivity reactions
Serious, life-threatening hypersensitivity reactions, sometimes fatal, have been reported with teicoplanin (e.g. anaphylactic shock). If an allergic reaction to teicoplanin occurs, treatment should be discontinued immediately and appropriate emergency measures should be initiated.
Teicoplanin must be administered with caution in patients with known hypersensitivity to vancomycin, as crossed hypersensitivity reactions, including fatal anaphylactic shock, may occur.

However, a prior history of "red man syndrome" with vancomycin is not a contraindication to the use of teicoplanin.

Infusion related reactions
In rare cases (even at the first dose), red man syndrome (a complex of symptoms including pruritus, urticaria, erythema, angioneurotic oedema, tachycardia, hypotension, dyspnoea) has been observed. Stopping or slowing the infusion may result in

cessation of these reactions. Infusion related reactions can be limited if the daily dose is not given via bolus injection but infused over a 30-minute period.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCAR) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal have been reported with the use of teicoplanin (see section 4.8). Acute generalized exanthematous pustulosis (AGEP) has also been reported with the use of teicoplanin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions (e.g. progressive skin rash often with blisters or mucosal lesions or pustular rash, or any other sign of skin hypersensitivity) and be closely monitored. If signs and symptoms suggestive of severe skin reactions appear, teicoplanin should be withdrawn and alternative treatment should be considered.

Spectrum of antibacterial activity
Teicoplanin has a limited spectrum of antibacterial activity (*Gram-positive*). It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a high suspicion that the most likely pathogen(s) would be suitable for treatment with teicoplanin.

The rational use of teicoplanin should take into account the bacterial spectrum of activity, the safety profile and the suitability of standard antibacterial therapy to treat the individual patient. On this basis it is expected that in most instances teicoplanin will be used to treat severe infections in patients for whom standard antibacterial activity is considered to be unsuitable.

Thrombocytopenia
Thrombocytopenia has been reported with teicoplanin (see section 4.8). Periodic haematological examinations, including complete blood count, are recommended during treatment.

Nephrotoxicity
Nephrotoxicity and renal failure have been reported in patients treated with teicoplanin (see section 4.8). Patients with renal insufficiency in those receiving the high loading dose regimen of teicoplanin, and those receiving teicoplanin in conjunction with or sequentially with other medicinal products with known nephrotoxic potential (*e.g.* aminoglycosides, colistin, amphotericin B, ciclosporin, and cisplatin) should be carefully monitored, and should get auditory tests (see "Ototoxicity" below).
Since teicoplanin is mainly excreted by the kidney, the dose of teicoplanin must be adapted in patients with renal impairment (see section 4.2).

Ototoxicity
As with other glycopeptides, ototoxicity (deafness and tinnitus) has been reported in patients treated with teicoplanin (see section 4.8). Patients who develop signs and symptoms of impaired hearing or disorders of the inner ear during treatment with teicoplanin should be carefully evaluated and monitored, especially in case of prolonged treatment and in patients with renal insufficiency. Patients receiving teicoplanin in conjunction with or sequentially with other medicinal products with known nephrotoxic and/or neurotoxic/ototoxic potential (*e.g.* aminoglycosides, colistin, amphotericin B, ciclosporin, cisplatin, furosemide and ethacrynic acid) should be carefully monitored and the benefit of teicoplanin evaluated if hearing deteriorates.

Special precautions must be taken when administering teicoplanin in patients who require concomitant treatment with ototoxic and/or nephrotoxic medicinal products for which it is recommended that regular haematology, liver and kidney function tests are carried out.

Superinfection
As with other antibiotics, the use of teicoplanin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed.

Teicoplanin and aminoglycoside solutions are incompatible and must not be mixed for injection; however, they are compatible in dialysis fluid and may be freely used in the treatment of CAPD-related peritonitis. Teicoplanin should be used with care in

conjunction with or sequentially with other medicinal products with known nephrotoxic and/or neurotoxic/ototoxic potential. These include *e.g.* aminoglycosides, colistin, amphotericin B, ciclosporin, cisplatin, furosemide, and ethacrynic acid (see section 4.4 "Nephrotoxicity" and "Ototoxicity"). However, there is no evidence of synergistic toxicity in combinations with teicoplanin.

In clinical studies, teicoplanin has been administered to many patients already receiving various medications including other antibiotics, antihypertensives, anaesthetic agents, cardiac medicinal products and antidiabetic agents without evidence of adverse interaction.

Paediatricpopulation
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are a limited amount of data from the use of teicoplanin in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3): in rats there was an increased incidence of stillbirths and neonatal mortality. The potential risk for humans is unknown.
Therefore, teicoplanin should not be used during pregnancy unless clearly necessary. A potential risk of inner ear and renal damage to the foetus cannot be excluded (see section 4.4).

Breast-feeding
It is unknown whether teicoplanin is excreted in human milk. There is no information on the excretion of teicoplanin in animal milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with teicoplanin should be made taking into account the benefit of breast-feeding to the child and the benefit of teicoplanin therapy to the mother.

Fertility
Animal reproduction studies have not shown evidence of impairment of fertility.

4.7 Effects on ability to drive and use machines

Teicoplanin Hikma has minor influence on the ability to drive and use machines. Teicoplanin can cause dizziness and headache. The ability to drive or use machines may be affected. Patients experiencing these undesirable effects should not drive or use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions
In the table below all the adverse reactions, which occurred at an incidence greater than placebo and more than one patient are listed using the following convention:
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.

System organ class	**Common (≥1/100to <1/10)**	**Uncommon (≥1/1,000to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**	**Not known (can not be estimated from available data)**
Infections and infestations			Abscess		Superinfection (overgrowth of non-susceptible organisms)
Blood and the lymphatic system disorders		Leucopenia, thrombocytopenia, eosinophilia			Agranulocytosis,neutropenia, pancytopenia
Immune system disorders		Anaphylactic reaction (anaphylaxis) (see section 4.4)			DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), Anaphylactic shock (see section 4.4)

Nervous system disorders		Dizziness, headache			Seizures
Ear and Labyrinth disorders		Deafness, hearing loss (see section 4.4), tinnitus, vestibular disorder			
Vascular disorders		Phlebitis			Thrombophlebitis
Respiratory, thoracic and mediastinal disorders		Bronchospasm			
Gastro-intestinal disorders		Diarrhoea, vomiting, nausea			
Skin and subcutaneous tissue disorders	Rash, erythema, pruritus		Red man syndrome (e.g. Flushing of the upper part of the body) (see section 4.4).		Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalized exanthematous pustulosis, erythema multiforme, angioedema, dermatitis exfoliative, urticaria (see section 4.4)
Renal and Urinary disorders		Blood creatinine increased			Renal failure (including renal failure acute) (see below description of selected adverse reactions)*
General disorders and administration site conditions	Pain, pyrexia				Injection site abscess, chills (rigors)
Investigations		Transaminases increased (transient abnormality of transaminases), blood alkaline phosphatase increased (transient abnormality of alkaline phosphatase)			

Description of selected adverse reactions

*Based on literature reports, the estimated rate of nephrotoxicity in patients receiving low loading dose regimen of average 6 mg/kg twice a day, followed by a maintenance dose of average 6 mg/kg once daily, is around 2%.

In an observational post-authorisation safety study which enrolled 300 patients with a mean age of 63 years (treated for bone and joint infection, endocarditis or other severe infections) who received the high loading dose regimen of 12 mg/kg twice a day (receiving 5 loading doses as a median) followed by a maintenance dose of 12 mg/kg once daily, the observed rate of confirmed nephrotoxicity was 11.0% (95% CI = [7.4%; 15.5%]) over the first 10 days. The cumulative rate of nephrotoxicity from the start of treatment up to 60 days after the last dose was 20.6% (95% CI = [16.0%; 25.8%]). In patients receiving more than 5 high loading doses of 12 mg/kg twice a day, followed by a maintenance dose of 12 mg/kg once daily, the observed cumulative rate of nephrotoxicity from the start of treatment up to 60 days after the last administration was 27% (95% CI = [20.7%; 35.3%]) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms
Cases of accidental administration of excessive doses to paediatric patients have been reported. In one case agitation occurred in a 29-day-old newborn who had been administered 400 mg intravenously (95 mg/kg).

Management
Treatment of teicoplanin overdose should be symptomatic.
Teicoplanin is not removed by haemodialysis and only slowly by peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glycopeptide Antibacterials, ATC code: J01XA 02

Mechanism of action
Teicoplanin inhibits the growth of susceptible organisms by interfering with cell-wall biosynthesis at a site different from that affected by beta-lactams. Peptidoglycan synthesis is blocked by specific binding to D-alanyl-D-alanine residues.

Mechanism of resistance
Resistance to teicoplanin can be based on the following mechanisms:

- Modified target structure: this form of resistance has occurred particularly in *Enterococcusfaecium*. The modification is based on exchange of the terminal D-alanine-D-alanine function of the amino-acid chain in a murein precursor with D-Ala-D-lactate, thus reducing the affinity to vancomycin. The responsible enzymes are a newly synthesised D-lactate dehydrogenase or ligase.
- The reduced sensitivity or resistance of staphylococci to teicoplanin is based on the overproduction of murein precursors to which teicoplanin is bound.

Cross-resistance between teicoplanin and the glycoprotein vancomycin may occur. A number of vancomycin-resistant enterococci are sensitive to teicoplanin (Van-B phenotype).

Susceptibility testing breakpoints
The MICs breakpoints according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), version 3.1, February 11, 2013 are displayed in the following table:

Microorganism	**Susceptible**	**Resistant**
Staphylococcus aureus[a]	≤2 mg/L	>2mg/ml
Coagulase-negative staphylococci [a]	≤4 mg/L	>4 mg/ml
Enterococcus spp.	≤2 mg/L	>2 mg/ml
Streptococcus spp. (A, B, C, G) [b]	≤2 mg/L	>2 mg/ml
Streptococcus pneumoniae[b]	≤2 mg/L	>2 mg/ml
Viridans group streptococci [b]	≤2 mg/L	>2 mg/ml
Gram-positive anaerobes except Clostridioides difficile	IE	IE
PK/PD (Non-species related) breakpoints [c,d]	IE	IE

[a] Glycopeptide MICs are method dependent and should be determined by broth microdilution (reference ISO 20776). *S.aureus*with vancomycin MIC values of 2 mg/ml are on the border of the wild type MIC distribution and there may be an impaired clinical response. The resistance breakpoint for *S.aureus*has been reduced to 2 mg/ml to avoid reporting of GISA

isolates intermediate as serious infections with GISA isolates are not treatable with increased doses of vancomycin or teicoplanin.
[b] Isolates with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.
[c] IE indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug.
[d]A MIC with a comment but without an accompanying S, I or R categorisation may be reported.

Pharmacokinetic/Pharmacodynamic relationship
Teicoplanin antimicrobial activity depends essentially on the duration of time during which the substance level is higher than the minimum inhibitory concentration (MIC) of the pathogen.

Susceptibility
The prevalence of resistance may vary geographically and over 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 of types of infections is questionable.

Commonly susceptible species ***Aerobic Gram-positive bacteria*** *Corynebacterium jeikeium*[a] *Enterococcus faecalis* *Staphylococcus aureus*(including methicillin-resistant strains) *Streptococcus agalactiae* *Streptococcus dysgalactiae* subsp. *equisimilis*[a] (Group C & G streptococci) *Streptococcus pneumoniae* *Streptococcus pyogenes* Streptococci in the viridans group [ab] ***Anaerobic Gram-positive bacteria*** *Clostridioides difficile*[a] *Peptostreptococcus spp.*[a]
Species for which acquired resistance may be a problem ***Aerobic Gram-positive bacteria*** *Enterococcus faecium* *Staphylococcus epidermidis* *Staphylococcus haemolyticus* *Staphylococcus hominis*
Inherently resistant bacteria All Gram-negative bacteria ***Other bacteria*** *Chlamydia spp.* *Chlamydophila spp.* *Legionella pneumophila* *Mycoplasma spp.*

[a]No current data were available when the tables were published. The primary literature, standard volumes and treatment recommendations assume sensitivity
[b]Collective term for a heterogeneous group of streptococcus species. Resistance rate can vary depending on the actual streptococcus species

5.2 Pharmacokinetic properties

Absorption
Teicoplanin is administered by parenteral route (intravenously or intramuscularly). After intramuscular administration, the bioavailability of teicoplanin (as compared to intravenous administration) is almost complete (90%). After six daily

intramuscular administrations of 200 mg the mean (SD) maximum teicoplanin concentration (Cmax) amounts to 12.1 (0.9) mg/L and occurs at 2 hours after administration.

After a loading dose of 6 mg/kg administered intravenously every 12 hours for 3 to 5 administrations, Cmax values range from 60 to 70 mg/L and Ctrough are usually above 10 mg/L. After an intravenous loading dose of 12 mg/kg administered every 12 hours for 3 administrations, mean values of Cmax and Ctrough are estimated to be around 100 mg/L and 20 mg/L, respectively.

After a maintenance dose of 6 mg/kg administered once daily Cmax and Ctrough values are approximately 70 mg/L and 15 mg/L, respectively. After a maintenance dose of 12 mg/kg once daily Ctrough values range from 18 to 30 mg/L.
When administered by oral route teicoplanin is not absorbed from the gastrointestinal tract. When administered by oral route at 250 or 500 mg single dose to healthy subjects, teicoplanin is not detected in serum or urine but only recovered in feces (about 45% of the administered dose) as unchanged medicinal product.

Distribution
The binding to human serum proteins ranges from 87.6 to 90.8% without any variation in function of the teicoplanin concentrations. Teicoplanin is mainly bound to human serum albumin. Teicoplanin is not distributed in red cells.
The volume of distribution at steady-state (Vss) varies from 0.7 to 1.4 ml/kg. The highest values of Vss are observed in the recent studies where the sampling period was superior to 8 days.
Teicoplanin distributed mainly in lung, myocardium and bone tissues with tissue/serum ratios superior to 1. In blister fluids, synovial fluid and peritoneal fluid the tissue/serum ratios ranged from 0.5 to 1. Elimination of teicoplanin from peritoneal fluid occurs at the same rate as from serum. In pleural fluid and subcutaneous fat tissue the tissue/serum ratios are comprised between 0.2 and 0.5. Teicoplanin does not readily penetrate into the cerebrospinal fluid (CSF).

Biotransformation
Unchanged form of teicoplanin is the main compound identified in plasma and urine, indicating minimal metabolism. Two metabolites are formed probably by hydroxylation and represents 2 to 3% of the administered dose.

Elimination
Unchanged teicoplanin is mainly excreted by urinary route (80% within 16 days) while 2.7% of the administered dose is recovered in feces (via bile excretion) within 8 days following administration. Elimination half-life of teicoplanin varies from 100 to 170 hours in the most recent studies where blood sampling duration is about 8 to 35 days.
Teicoplanin has a low total clearance in the range of 10 to 14 ml/h/kg and a renal clearance in the range of 8 to 12 ml/h/kg indicating that teicoplanin is mainly excreted by renal mechanisms.

Linearity
Teicoplanin exhibited linear pharmacokinetics at dose range of 2 to 25 mg/kg.

Special populations

- *Renal impairment:*

As teicoplanin is eliminated by renal route, teicoplanin elimination decreases according to the degree of renal impairment. The total and renal clearances of teicoplanin depends on the creatinine clearance.

- *Elderly patients:*

In the elderly population the teicoplanin pharmacokinetics is not modified unless in case of renal impairment.

- *Paediatric population*

A higher total clearance (15.8 ml/h/kg for neonates, 14.8 ml/h/kg for a mean age 8 years) and a shorter elimination half-life (40 hours neonates; 58 hours for 8 years) are observed compared to adult patients.

5.3 Preclinical safety data

Following repeated parenteral administration to the rat and dog, effects on the kidney were observed and were shown to be dose-dependent and reversible. Studies to investigate the potential to cause ototoxicity in the guinea-pig indicate that a mild impairment of cochlear and vestibular function is possible, in the absence of morphological damage.

Subcutaneous administration of teicoplanin at up to 40 mg/kg/day did not affect male and female fertility in the rat. In embryofetal development studies, no malformations were observed following subcutaneous administration of up to 200 mg/kg/day in the rat and intramuscular administration up to 15 mg/kg/day in the rabbit. However, in the rat, there was an increased incidence of stillbirths at doses of 100 mg/kg/day and above and neonatal mortality at 200 mg/kg/day. This effect was not reported at 50 mg/kg/day A peri and postnatal study in rats showed no effects on the fertility of the F1 generation or on the survival and development of the F2 generation following subcutaneous administration of up to 40 mg/kg/day.

Teicoplanin did not show any potential to cause antigenicity (in mice, guinea-pigs or rabbits), genotoxicity or local irritancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

6.2 Incompatibilities

Teicoplanin and aminoglycoside are incompatible when mixed directly and must not be mixed before injection.

If teicoplanin is administered in combination therapy with other antibiotics, the preparation must be administered separately.

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:
3 years

Shelf life of reconstituted solution:
Chemical and physical in-use stability of the reconstituted solution prepared as recommended has been demonstrated for 24 hours at 2 to 8°C.
From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Shelf life of diluted medicinal product:
Chemical and physical in-use stability of the reconstituted solution prepared as recommended has been demonstrated for 24 hours at 2 to 8°C.
From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Powder as packaged for sale:
This medicinal product does not require any special storage condition.

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

6.5 Nature and contents of container

Colourless, Type I glass vials of 10 ml for Teicoplanin 200 mg or 20 ml for Teicoplanin 400 mg, closed with a bromobutyl rubber stopper and sealed with an aluminium/plastic "flip-off cap".

Pack size: 1 or 10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is for single use only.

Preparation of reconstituted solution:

- The powder should be reconstituted with 3.14 ml of water for injections.
- Gently roll the vial between the hands until the powder is completely dissolved. If the solution does become foamy, then it should be left to stand for about 15 minutes. Only clear and yellowish solutions should be used. The reconstituted solutions will contain 200 mg of teicoplanin in 3.0 ml and 400 mg in 3.0 ml.

Nominal teicoplanin content of vial	200 mg	400 mg
Volume of powder vial	10 ml	20 ml
Volume containing nominal teicoplanin dose (extracted by 5 mL syringe and 23 G needle)	3.0 ml	3.0 ml

The reconstituted solution may be injected directly or alternatively further diluted, or orally administered.
Preparation of the diluted solution before infusion:
Teicoplanin Hikma can be administered in the following infusion solutions:

- sodium chloride 9 mg/ml (0.9%) solution
- Ringer solution
- Ringer-lactate solution
- 5% dextrose injection
- 10% dextrose injection
- 0.18% sodium chloride and 4% glucose solution
- 0.45% sodium chloride and 5% glucose solution
- Peritoneal dialysis solution containing 1.36% or 3.86% glucose solution.

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

7 MARKETING AUTHORISATION HOLDER

Hikma Farmacêutica (Portugal) S.A.
Estrada do Rio da Mó,
no 8, 8A e 8B - Fervença,
Terrugem-SNT
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Portugal

8 MARKETING AUTHORISATION NUMBER

PA1217/010/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th April 2018

10 DATE OF REVISION OF THE TEXT