EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report pursuant to Article 30 of Directive 2001/83/EC

Targocid and associated names

INN of the active substance: teicoplanin

Procedure no: EMEA/H/A-30/1301

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 25 October 2011 the European Commission on behalf of all marketing authorisation holders presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products:

Targocid and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the November 2011 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Dr Ian Hudson as rapporteur and Dr Harald Enzmann as co-rapporteur. The co-rapporteurship was transferred to Dr Martina Weise as of 4 March 2013.

Targocid medicinal products are registered in the following EU Member States: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and United Kingdom and also in Norway.

Targocid medicinal products are currently not registered in the following EU Member States: Cyprus, Estonia, Latvia and Lithuania.

2. Scientific discussion

2.1. Introduction

Teicoplanin is a glycopeptide antibiotic produced by fermentation of *Actinoplanes teichomyceticus* with *in-vitro* bactericidal activity against aerobic and anaerobic gram-positive bacteria. It is a complex antibiotic, consisting of six closely related glycopeptide subcomponents (A2-1, A2-2, A2-3, A2-4 and A2-5 forming A2 group, and A3) as defined in the current European Pharmacopoeia (Ph. Eur.) monograph for teicoplanin. Some of the subcomponents are in fact groups of smaller peaks, namely A2-1, A2-3, A2-5 and A3. The subcomponents are separated by HPLC according to their polarity.

Currently there are only two known glycopeptide antibiotics: vancomycin and teicoplanin.

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

Teicoplanin is available as sterile lyophilized powder for injection, each vial containing 100 mg, 200 mg or 400 mg of teicoplanin as the active ingredient. The solvent provided for the intravenous (IV) or intramuscular (IM) administration consists of sterile water for injection.

Due to the divergent national decisions taken by Member States concerning the authorization of the Targocid and associated names, the European Commission notified the EMA of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised SmPCs for the above-mentioned products and thus to harmonise the SmPCs across the EU.

2.2. Critical Evaluation

2.2.1. Quality aspects

2.2.1.1. Introduction

Sanofi-Aventis took the opportunity to harmonise the Quality dossier for Targocid and associated names as part of this Article 30 referral procedure.

The harmonised dossier was provided for the active substance (teicoplanin) and for products containing this substance: Targocid 100, 200 mg and 400 mg powder for solution for injection/infusion and Targocid 100, 200 mg and 400 mg powder and solvent for solution for injection/infusion.

Module 3 was also updated to reflect additional data on characterisation of individual subcomponents which were collected by the MAH since Targocid was authorised, and to upgrade the dossier in general.

2.2.1.2. Active Substance

Information on the active substance was submitted in an ASMF. The MAH submitted sufficient information on nomenclature, structure and general properties of the active substance. Detailed information on the starting materials, fermentation and purification process was provided on request and was found acceptable. The fermentation process has been modified since the initial marketing authorisation application with respect to the production strain (early in the product lifecycle), fermentation media and isolation/purification process; however, no significant changes were observed with respect to the quality/subcomponent profile of the active substance. It can be concluded that results of more than 800 manufactured batches prove good consistency of the manufacturing process.

Harmonisation of the active substance specification was also needed as tighter limits for the individual subcomponents were approved in some Member States, compared to the current Ph. Eur. monograph. The number of individual subcomponents was expanded to include all teicoplanin-like substances which contain the same core glycopeptide structure. The spectrum of teicoplanin subcomponents has been better characterised. Limits for all individual subcomponents were established based on batch data at release and during stability testing.

Potency of teicoplanin active substance is tested according to Ph. Eur. monograph for microbiological assay of antibiotics. Satisfactory information was presented for the reference standard.

A valid TSE certificate was provided for the active substance.

2.2.1.3. Finished Product

More data was provided on manufacturing process validation, with particular emphasis on sterilisation process. Media fill simulation was conducted successfully and described in sufficient level of detail.

The finished product specifications were discussed extensively during the procedure. The MAH presented batch results for the finished product at release and during stability studies. Degradation pattern of teicoplanin is well understood – A2 group degrades to A3 group – and the degradation products remain pharmacologically active. Therefore, limits for individual subcomponents are not needed for the finished product; only A2 and A3 groups need to be monitored. Potency of teicoplanin in the finished product is tested according to Ph. Eur. monograph for microbiological assay of antibiotics.

More detailed description of the analytical methods was introduced in the dossier.

The dossier was updated to include compatibility studies with various types of diluents, PVC bags and syringes, together with in-use stability data.

The strengths of teicoplanin finished product are conventionally declared and prescribed in terms of mass (e.g. 200 mg and 400 mg), but given the variability of the active substance, it is the potency of the finished product, as determined by microbiological assay and declared in IU (e.g. 200,000 IU or 400,000 IU), that determines the quantitative amount of active substance in the finished product.

The Ph. Eur. monograph specifies a minimum potency 900 IU/mg. However, the convention of declaring the strength of the finished product in terms of mass (mg) is based on a nominal fixed potency of 1000 IU/mg for the active substance. The required quantity of the active substance per vial is formulated by taking into consideration the actual microbiological potency (IU/mg) of the active substance, to achieve the target activity of 200,000 IU or 400,000 IU per vial. The product information was therefore updated to declare the qualitative and quantitative details of the active substance in terms of mass and IU: each vial contains 200mg (or 400) mg teicoplanin equivalent to 200,000 IU (or 400,000 IU).

2.2.2. Discussion and Conclusions on quality

As a result of this harmonisation procedure, Module was 3 substantially updated and revised to include data which has become available during the years since the first marketing authorisation. The manufacture and control of both the active substance and the finished product comply with CHMP/ICH guidelines. Quality of the product is considered satisfactory.

2.2.3. Clinical aspects

2.2.3.1 Section 4.1 – Therapeutic Indications

Treatment of infections caused by Gram-positive microorganisms
The clinical development focussed on the susceptibility of gram-positive bacteria to teicoplanin and not on specific indications. In line with the CHMP Guideline on the Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95 rev 2), it was considered acceptable to further qualify the indications.

Also in line with the above-mentioned CHMP Guideline, section 4.1 has been simplified, and information on the need for co-administration with other antibacterial agents, the rational and appropriate use and antibacterial spectrum has been mentioned in sections 4.2, 4.4 and 5.1.

The efficacy of teicoplanin in the treatment of Gram-positive infections was investigated in the following clinical studies:

Open-label non-comparative therapeutic studies

- *European Multicentre Study*

A European Multicentre Study was conducted in eight member states (Austria, Belgium, France, Germany, Greece, Ireland, Italy, and UK) and Switzerland. In this study teicoplanin was administered to 1431 patients (adults, the elderly and children) with suspected Gram-positive infection.

Most of the patients included in these studies had suspected gram-positive infections from different sites with the majority of them having skin and soft tissues infections (SSTIs), septicaemia and bone and joint infections. There were also a few cases of endocarditis, respiratory tract infections and urinary tract infections.

Gram-positive bacteria accounted for 93% of isolates, including 72.6% of Staphylococci (79% of *Staphylococcus aureus* (*S. aureus*) and 24% of Methicillin-resistant *Staphylococcus aureus* (MRSA)), and 25.4% of Streptococci. Only 29 isolates were other Gram-positive bacteria. Severe infections such as endocarditis, “septicaemia”, bone and joint infections, and meningitis accounted for 33% of cases.

Most patients received an initial teicoplanin loading dose of 400 mg of teicoplanin (6 mg/kg) IV on the first day, followed by 200 mg IV or IM daily. In case of severe infections, the dose of 400 mg was usually continued beyond the first day. The mean duration of treatment was 14 days. Elderly patients received the same dosage as for younger adults. Of 1431 patients, 394 received associated antibiotics.

The clinical cure and improvement rates in evaluable cases were 92%, ranging from 95% (SSTIs) to 83% (endocarditis), and with rates of 90% (septicaemia and lower respiratory tract infections) and 87% (bone and joint infections) in between.

Overall bacteriological success rates (elimination or marked reduction) in evaluable cases were 79%, ranging from 84% (septicaemia) to 71% (bone and joint infections), and with rates of 81% (SSTIs and endocarditis) and 76% (lower respiratory tract infections) in between. When analysed by type of bacteria, bacteriological success rates were 85% for *S. aureus,* with similar figures between MRSA (86.1%) and methicillin-sensitive *Staphylococcus aureus* (MSSA) (84.2%), 96% for nosocomial coagulase negative staphylococcal (CoNS) infections, and 98% for *E. faecalis*. The minimum inhibitory concentration (MIC) was determined for 762 Gram-positive isolates; some 90% of the MICs were 1 mg/L or lower; only 9 isolates had a MIC above 5 mg/L.

- *US Open Multicentre Study*

This open label non-comparative study conducted at six centres in the US included 41 adult patients hospitalized for severe Gram positive infections. Teicoplanin was administered IV or IM.

There were 9 bone and joint infections (31.0%), 8 SSTIs (27.6%), 6 bacteremia/ septicemia (20.6%), 5 endocarditis (17.2%), and one lower respiratory tract infections (3.4%).

Most isolates were Staphylococci (28 isolates, including 10 methicillin-resistant isolates) and Streptococci (4 isolates).

Seventeen patients were considered clinically cured and 6 were considered improved, yielding a clinical cure and improvement rate of 79% (23/29 patients).

Regarding bacteriological outcome, the pathogen was eliminated in 20 patients, and reduced in 3 patients, yielding a bacteriological success (elimination or marked reduction) rate of 79% (23/29 patients). Recurrence was observed in one case, the pathogen persisted in another case and the bacteriological outcome was not determined in 4 patients.

Comparative therapeutic studies

Comparative studies were conducted for the initial marketing authorisation application at 12 centres, including 349 patients with Gram-positive infections; 181 of which were treated with teicoplanin and 168 were treated with a comparator. This is a review of the comparative studies conducted with teicoplanin.

The comparative regimens included isoxazolyl penicillins with or without sodium fusidate (64 cases), vancomycin with or without netilmicin (62 cases), or ceftazidime plus amikacin (42 cases).

The main sites of infection were skin and soft tissue infections, “septicaemia”, lower respiratory tract infections (LRTI), bone and joint infections, and endocarditis, and the main reported isolates were CoNS and *S. aureus.*

Overall, the clinical efficacy estimates (cure rate and improvement) were 84.3% for teicoplanin versus 92.3% for penicillins, and 77.8% for teicoplanin versus 79.6% for vancomycin. Using the Kolmogorov-Smirnov test for the individual centres, there was no significant difference in overall efficacy between teicoplanin and penicillins (k=0.6277) or between teicoplanin and vancomycin (k=0.1928).

The bacteriological efficacy estimates (elimination) were 76.1% for teicoplanin versus 82.2% for penicillins, and 76.5% for teicoplanin versus 70.8% for vancomycin. Using Fisher's (2x2) exact probability test, there was no significant difference in overall elimination rates between teicoplanin and vancomycin (p=0.6818).

In conclusion the comparative therapeutic studies show that the clinical cure and improvement rate of teicoplanin and the penicillins, or teicoplanin and vancomycin were not significantly different. Similarly, there were no significant differences in bacteriological outcome. In comparison with penicillins, the results for teicoplanin were considered more satisfactory, when the cases with organisms resistant to methicillin were excluded from entry to the study.

Literature references

The results from the literature references submitted in the initial authorisation, show clinical cure rates ranging from about 72.8 to 87.6%.

The current status, rationale and the evidence for the treatment of the following infections caused by Gram-positive microorganisms are discussed below:

- Skin and soft tissue infections (SSTI)

The indication for the treatment of SSTI caused by susceptible Gram-positive bacteria, including those resistant to other antibiotics (such as methicillin and cephalosporins) has been approved in all EU countries, although not necessarily listed in countries where the body site of infection is not mentioned in the SmPCs, such as Denmark, Ireland, Italy, Norway and Sweden.

The clinical and bacteriological efficacy of teicoplanin was shown in SSTIs (37.4% of all infection sites) in the European Multicentre Study. The SSTIs mainly included erysipelas, cellulitis, abscess, wound infection, and furonculosis. The clinical success rates were 95% of evaluable cases, and bacteriological success (elimination or marked reduction) rates were 81%.

The CHMP concluded that teicoplanin should be indicated in complicated SSTIs i.e. severe cases, but not for the treatment of minor SSTIs in line with the British Society for Antimicrobial Chemotherapy (BSAC) guideline, which does not recommend systemic antibiotics for the treatment of minor SSTIs.

- Bone and joint infections

The indication for the treatment of bone and joint infections caused by susceptible Gram-positive bacteria, including those resistant to other antibiotics (such as methicillin and cephalosporins) is approved in all EU countries, except in Finland, where the indication for Gram-positive infections only is mentioned in the SmPC. The indication is restricted to osteomyelitis in Belgium, Bulgaria, The Netherlands, Slovakia and Spain. In Austria, Germany and Greece osteomyelitis has been added to the SmPCs as an example of bone infections. In Denmark, Ireland, Italy, Norway and Sweden the body site of infection is not stated.

The clinical and bacteriological efficacy of teicoplanin was shown in both the European Multicentre study and the US open multicentre study.

As agreed by the CHMP, the indication for the treatment of bone and joint infections has been maintained without specifically mentioning osteomyelitis, septic arthritis and prosthetic infections.

- Pneumonia and respiratory tract infections

The indication for the treatment of respiratory tract infections caused by susceptible Gram-positive bacteria, including those resistant to other antibiotics (such as methicillin and cephalosporins) is approved in all EU countries, except in Finland where the indication for pathogens Gram-positive infections only is mentioned in the SmPC. In France, Hungary, Malta, The Netherlands, Poland,

Portugal, Romania, Slovenia and UK, the SmPCs list “Lower respiratory tract or pulmonary tract” in the “Indication” section. In Denmark, Ireland, Italy, Norway and Sweden the body site of infection is not stated.

In the European multi-centre study, approximately 9% of the subjects enrolled had lower respiratory tract infections. The clinical cure and improvement rate was about 90% and bacteriological success rate was 76%.

In the comparative study by Cepeda et al (2004)[1], in which teicoplanin was compared to Linezolid, 29 patients with lower respiratory tract infection were included, and the clinical success rates were 82.8% in teicoplanin-treated patients, and microbiological efficacy was 68.2%.

In the study by Wilcox et al (2004)[2], an open label study which compared linezolid with teicoplanin, 27% of the subjects included had pneumonia and the clinical success rate was 92.9% for teicoplanin. However in this study, bacteria eradication rates were higher in the linezolid group (81.9% versus 69.8%).

The results from these various studies suggest that teicoplanin has a place in the management of pneumonia. The CHMP agreed that teicoplanin can be indicated for the treatment of pneumonia (hospital acquired and community acquired pneumonia) without restricting its use according to the pathogen. However due to its limited spectrum of antibacterial activity, a cross reference to section to 4.4 commenting on the limited spectrum of antibacterial use and its rational use has been included.

- Bacteraemia/ Septicaemia / Sepsis

The indication for the treatment of septicaemia caused by susceptible Gram-positive bacteria including those resistant to other antibiotics (such as methicillin and cephalosporins) is approved in all SmPCs, except in Denmark, Ireland, Italy, Norway and Sweden where the body site of infections is not mentioned in the SmPCs.

As ‘Sepsis’ is generally a secondary condition to a primary site infection, it was not considered to be acceptable as a stand-alone indication, and was therefore deleted from the list of indications. Instead, the indication for bacteraemia has been included in accordance with CHMP Guideline on the Evaluation of Medicinal Products Indicated for the Treatment of Bacterial Infections (CPMP/EWP/558/95 rev 2).

- Urinary tract infections (UTI)

The indication for the treatment of UTI caused by susceptible Gram-positive bacteria, including those resistant to other antibiotics (such as methicillin and cephalosporins) is approved in all EU countries, except in Finland, Denmark, Ireland, Italy, Norway and Sweden as the body site of infection is not stated. In France and Hungary, the SmPCs list “Upper and Lower Urinary Tract Infections, with or without complications” and “complicated renal and Urinary Tract Infection”, respectively.

In the European Multicentre Study, the clinical and bacteriological efficacy of teicoplanin has been shown in UTI (8% of all infection sites).

Considering that UTIs are mainly caused by gram-negative infections, the MAH was of the view that teicoplanin has a limited role in the management of UTIs. The indication was therefore restricted to complicated urinary tract infections, which was accepted by the CHMP.

[1] Cepeda J A, Whitehouse T, Cooper B, et al. Linezolid versus teicoplanin in the treatment of Gram-positive infections in the critically ill: a randomized, double-blind, multicentre study. J Antimicrob Chemother 2004; 53: 345-55.
[2] Wilcox M, Nathwani D, Dryden M. Linezolid compared with teicoplanin for the treatment of suspected or proven Gram-positive infections. J Antimicrob Chemother 2004; 53: 335-44.

- Infective endocarditis

The indication for the treatment of endocarditis caused by susceptible Gram-positive bacteria, including those resistant to other antibiotics (such as methicillin and cephalosporins) is approved in all EU countries. In Denmark, Ireland, Italy, Norway and Sweden no body sites of infection are listed in the SmPCs.

No specific study has been conducted by the MAH in support of this indication. However a few cases of endocarditis were included in the open-label studies conducted in support of the initial marketing authorisations. In one study the clinical outcome for endocarditis was 83% (excluding patients considered as non-evaluable). According to the report, endocarditis contributed to more failures proportionally, than the other main infection sites. This was considered to be the result of using a low dose of teicoplanin and not using other concomitant antibiotics.

The MAH has provided evidence from publications in support of the use of teicoplanin in combination with other anti-microbial agents such as aminoglycosides. Therefore the CHMP was in agreement with the MAH's proposal that teicoplanin should be used in combination with other anti-microbial agents when appropriate, as cross-referenced in section 4.4.

- Peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD)

The indication in peritonitis associated with CAPD is already included in the SmPC of most of the member states but not listed in Finland and Germany, although the indication for pathogens causing Gram-positive infections is mentioned in these SmPCs.

There is evidence to suggest that teicoplanin is effective in this indication. In a Cochrane meta-analysis of randomised controlled trials (RCT) in adults and children with CAPD-associated peritonitis, no superior antibiotic agent or combination of agents were identified. Primary response and relapse rates did not differ between intraperitoneal (IP) glycopeptide-based regimens compared to first generation cephalosporin regimens, although glycopeptide regimens were more likely to achieve a complete cure, and primary treatment failure was less likely to occur with teicoplanin than vancomycin (Wiggins et al. 2008)[3]. Considering all the available information, the CHMP agreed that this indication should remain in the harmonised SmPC.

Prophylaxis of infections caused by Gram-positive microorganisms

Four prophylaxis comparative studies were conducted:

- one study in two phases in cardiovascular surgery, of which only phase 1 was completely analysed
- one study in orthopaedic surgery
- two studies in dental surgery

The studies provided in support of prophylactic use in cardiac surgery suggest that teicoplanin was not effective in preventing post-operative infections.

The indication for the prophylactic use of teicoplanin in orthopaedic surgery was not adequately justified. The data was not considered to be sufficiently robust as they were open-labelled comparative studies that did not demonstrate that teicoplanin was better than the comparators. Therefore the indication for the prophylactic use of teicoplanin was not considered to be acceptable by the CHMP.

No data in support of the use of teicoplanin in the prevention of infective endocarditis was submitted.

[3] Wiggins KJ, Cochrane Collaboration review and meta-analysis 2008.

Regarding dental surgery prophylaxis, the results suggested that teicoplanin could be useful. However this indication is not recommended in current guidelines on the management of infective endocarditis as pointed out by the MAH, and therefore the deletion of this indication was considered to be acceptable by the CHMP.

Treatment of Clostridium difficile infection-associated diarrhoea and colitis

The indication "antibiotic-associated diarrhoeal caused by *Clostridium difficile*" is found in the SmPCs in Denmark and Greece but not in Austria, Belgium, Finland, France, Hungary, Ireland, Italy, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Sweden and UK.

In the clinical development program of teicoplanin, three open, non-controlled studies were conducted with teicoplanin IV formulation administered orally for antibiotic-associated diarrhea (AAD) and pseudomembranous colitis (PMC) caused by *C. difficile*: two studies in Italy and one in the United Kingdom.

In all (pooled data), 72 episodes of infection were treated in 71 adult patients. The results from these three studies showed that teicoplanin achieves an overall clinical and bacteriological response rate of nearly 90% in culture and toxin positive patients.

The pharmacokinetics of teicoplanin for the treatment of *Clostridium difficile* was investigated a study. This indication was considered to be acceptable by the CHMP as it appears that teicoplanin is not absorbed to a great extent from the gastro-intestinal tract.

Paediatric population

Section 4.1 of the SmPC does not include the paediatric population in all MS. In most of them the posology for children, neonates and new-borns is mentioned in section 4.2.

Four clinical studies provided data in children treated with specific paediatric protocols, and one study that included 7 neonates. Patients were aged 1 day to 15 years; the majority had severe infection and a high proportion of neutropenic patients had pyrexia of unknown origin.

These studies were small and clinical experience with teicoplanin in neonates, infants and children is limited. However the available data suggest that teicoplanin administered IV or IM at dosages of 10 mg/kg every 12 hours for 1 to 5 doses (loading dosage), then 6 to 10 mg/kg once daily, is effective in the treatment of Gram-positive infections such as septicaemia, skin and soft tissue infections, bone and joint infections, lower respiratory tract infections, and in neutropenia and fever in children. In keeping with the adult studies, the clinical cure was > 80%.

Since teicoplanin is already used in children in most member states and clinical guidelines recommend its use in children, the indication for the use of teicoplanin in children, as well as in neonates and infants was supported by the CHMP.

2.2.3.2 Section 4.2 - Posology and method of administration

Posology

Targocid is available in dosages of 100 mg, 200 mg and 400 mg. As mentioned in the SmPC proposed by the MAH, a dose of 6mg/kg is equal to 400mg in adults, and 12mg/kg is equal to 800mg.

Teicoplanin antimicrobial activity is thought to depend on trough concentrations being higher than MIC of particular pathogens, and also dependent on the duration of time during which trough concentrations remain higher than MIC. An optimal serum trough concentration for teicoplanin is needed as teicoplanin exhibits time-dependent anti-bacterial activity. The MAH has proposed that a trough plasma concentration of 10mg/l (when measured by high performance liquid chromatography)

should be maintained for most infections, and that higher concentrations of 15 to 30mg/l for endocarditis, septic arthritis and osteomyelitis should be considered for severe infections.

Based on the Monte Carlo simulations conducted by Yamada et al[4] the MAH has proposed a loading dose of 6mg/kg bid for 3 administrations for most infections, and 12mg/kg bid for 3 to 5 administrations for bone and joint infections and infective endocarditis. The loading dose of 12mg/kg bid is in line with what is currently recommended in the SmPCs in France and Finland. A warning has been included in sections 4.4 and 4.8 of the SmPC that patients should be especially monitored for adverse reactions when the higher dosage of 12mg/kg bid is administered.

Since safety data for the loading dose of 12mg/kg bid (24mg/kg/day) is limited, the MAH has agreed to the request made by the CHMP to perform an appropriate post authorisation safety study (PASS) to evaluate the safety of the higher loading dose of Targocid 12mg/kg bid (24mg/kg/day). The MAH has also agreed to the request made by the CHMP to submit a risk management plan (in which the PASS protocol will be included), in particular, to adequately address the important potential risk of the increased frequency of nephrotoxicity and other serious adverse reactions with loading doses of Targocid 12mg/kg bid (24mg/kg/day).

As is the current practice in some member states, the maintenance dose of 6-12mg/kg od depending on the type of infection was maintained: 6mg/kg od for complicated skin, soft tissue and urinary tract infections and pneumonia and 12mg/kg od for bone and joint infections and endocarditis.

The overall duration of treatment with teicoplanin has not been given precisely since it should be adjusted individually, according to the underlying type and severity of infection, the clinical response of the patient and patient factors such as age and renal function. For infective endocarditis, the CHMP considered that 21 days would be the minimum period of use, and that treatment beyond of 4 months should be avoided.

Method of administration

Administration of teicoplanin as a bolus or 30 minute administration is accepted at present in most member states. Although no pharmacokinetic evidence has been provided, the rationale for having a bolus alternative to the 30-minute infusion to facilitate use in out-patients settings was considered to be acceptable by the CHMP.

Targocid is not administered by the intraventricular route and is mentioned as a special warning in section 4.4.

Measurement of serum concentration

The information on the measurement of teicoplanin trough serum concentrations by High Performance Liquid Chromatography (HPLC) and Fluorescence Polarization Immunoassay (FPIA) method was considered to be acceptable by the CHMP.

Since it is proposed that the loading dose should be administered 3 to 5 times, it has been stated in the SmPC that trough serum concentrations should be monitored on completion of the loading dose regimen. Measurement of trough serum concentrations is also recommended at least once a week during the maintenance treatment.

[4] Yamada T , Nonaka T Yano T, Kubota T, Egashira N, Kawashiri T, Oishi R, Yamada T, Kawashiri T, Oishi R (2012). Simplified dosing regimens of teicoplanin for patient groups stratified by renal function and weight using Monte Carlo simulation. International Journal of Antimicrobial Agents 40 (2012) 344– 348.

Paediatric population

In the four published studies of the initial dossier, 213 evaluable episodes of infection have been treated in 211 patients aged 1 day to 15 years, the majority with severe infections. Teicoplanin dose regimens across studies ranged from 6 mg/kg unit dose to a loading dose of 10 mg/kg every 12 hours for 3 doses followed by 10 mg/kg daily maintenance dose.

Although no PK-PD modelling has been done, the proposed posology for children is based on Monte Carlo simulations conducted by Lucas et al in 2004 [5]and Reed in 1997[6], which was considered to be acceptable by the CHMP.

Adults and elderly patients with impaired renal function

The requirement for the adjustment of the dosage in patients with renal impairment, from the fourth day of treatment with teicoplanin has been included (see section 2.2.3.4).

2.2.3.3 Section 4.3 - Contraindications

The MAH has amended section 4.3 only including hypersensitivity to teicoplanin (or to any of the excipients).

2.2.3.4 Section 4.4 - Special warnings and precautions for use

The wording of the core safety profile (CSP), currently approved in the context of the PSUR work-sharing procedure number GR/H/PSUR/0001/001, was proposed by the MAH for the harmonised SmPC. All the important safety information that has been included in the SmPC has been listed in order of importance.

Hypersensitivity reactions, anaphylactic shock

A cumulative review was submitted by the MAH, of all cases in the Standardized MedDRA Query (SMQ) Anaphylactic Reaction (Narrow), which includes the Preferred Terms (PTs) of Anaphylactic reaction; Anaphylactic shock; Anaphylactoid reaction; Circulatory collapse; Shock; Type I hypersensitivity; Anaphylactoid shock; Anaphylactic transfusion reaction; First use syndrome; Kounis syndrome. It was concluded that in 9 fatal cases a plausible association of teicoplanin could be considered. Of the 9 cases with fatal outcomes, 2 patients were switched from vancomycin due to relatively benign allergic reactions and experienced a fatal anaphylactic shock following a single dose of teicoplanin.

Based on the review, the MAH proposed a modified warning regarding hypersensitivity reactions to address the fatal cases that have been reported and to strengthen the possibility of cross hypersensitivity to vancomycin.

Prior history of "Red Man Syndrome" with vancomycin is not considered to be a contradiction to the use of teicoplanin.

Infusion related reactions

Forty one cases of Red Man Syndrome (angioneurotic oedema, hypotension, dyspnoea) have been reported. A cumulative review on RMS supported a causal association between Red Man Syndrome and teicoplanin therapy, and its frequency was considered as “very rare”. Because of potential serious adverse reactions of Red Man Syndrome, a warning under the heading ‘Infusion related reactions’ has been included.

[5] Lucas JC, Karikas G, Gazouli M, et al. Pharmacokinetics of teicoplanin in an ICU population of children and infants. Pharm Res 2004; 21: 2064-71.
[6] Reed MD, Yamashita TS, Myers CM, et al. The pharmacokinetics of teicoplanin in infants and children. J Antimicrob Chemother 1997 ; 39: 789-96.

Severe bullous reactions

A cumulative SMQ (from IBD date of 01-Nov-1986 to 01-Nov-2011) of the MAHs global phamacovigilance database on severe cutaneous adverse reactions (Broad + Narrow) including Diagnoses and Symptoms was performed. From this query, a total of 25 cases coding Stevens-Johnson syndrome (SJS) and 23 cases coding toxic epidermal necrolysis (TEN) were retrieved.

Stevens-Johnson Syndrome (SJS)

Four SJS cases had a fatal outcome. All these 4 cases involved underlying multi-morbid conditions and were confounded by concomitant medication.

Toxic epidermal necrolysis (TEN)

Nine TEN cases had a fatal outcome. Multi-morbid condition(s) or risk factors for a fatal outcome occurred in 6 cases. Of the remaining 3 cases, one case was considered unrelated, as the possible skin manifestations preceded the start of teicoplanin, and 2 cases lacked sufficient data for a causal assessment. In addition, the latter cases involved multiple co-suspect drugs including medicines known to be causally associated with TEN.

Regarding the fatal SJS and TEN reported cases (except for the 3 TEN cases mentioned above) multi-morbid condition(s) risk factors associated with a fatal outcome was present in all the assessable cases. Thus based on the review carried out, a warning in section 4.4 on severe bullous skin reactions has been included by the MAH, where the occurrence of SJS and TEN is mentioned. This was considered to be acceptable by the CHMP.

Loading dose regimen

A clear warning has been included in the SmPC that patients should be especially monitored for adverse reactions when higher dosages of 12mg/kg bid (24mg/kg/day) are administered.

As mentioned above, the MAH has agreed to perform an appropriate post-authorisation safety study (PASS) to evaluate the safety of the higher loading dose of Targocid 12mg/kg bid (24mg/kg/day). The MAH has also agreed to submit a risk management plan (in which the PASS protocol will be included), in particular, to adequately address the important potential risk of increased frequency of nephrotoxicity and other serious adverse reactions with loading doses of 12mg/kg bid (24mg/kg/day).

In addition, information on the spectrum of antibacterial activity and rational use of teicoplanin was also included in this section.

No supportive data for the inclusion of the statement “convulsions after intraventricular administration” was retrieved. Nevertheless a warning has been added in this section that “Teicoplanin should not be administered by intraventricular route”.

Thrombocytopenia

A cumulative search in the MAH`s global pharmacovigilance database performed in May 2012 identified 347 serious associated, solicited and spontaneous cases of thrombocytopenia. Based on the review of cases of thrombocytopenia, the wording for the warning as proposed by the MAH is supported by the CHMP. As thrombocytopenia has been reported with teicoplanin, periodic haematological studies are recommended during treatment with teicoplanin.

Renal failure including renal failure acute

A cumulative search of the MAHs global pharmacovigilance database (up to 7 June 2012) using the MedDRA version 15.0 and the High Level Term (HLT) of Renal failure and impairment, including Diagnoses and Symptoms, was performed. From this query, a total of 254 cases (involving 269

events) were retrieved. Overall, the patients presented multiple morbidities; advanced age, multiple drug regimens (also involving known nephrotoxic drugs) and very severe infections.

A separate passage in section 4.4 with a heading “Nephrotoxicity” has been included, with a warning that renal failure has been reported with the use of teicoplanin. Patients with renal insufficiency and/or those receiving teicoplanin in conjunction or sequentially with other medicinal products with known nephrotoxic potential should be monitored carefully.

Deafness, hearing loss

A cumulative SMQ of the global pharmacovigilance database (up to 7-Jun- 2012) on Hearing Impairment (Narrow) including Diagnoses and Symptoms was performed. This query used the PSUR criteria; all spontaneous cases and all serious associated (to drug of interest) clinical trial cases were included.

From this query, a total of 87 cases (involving 99 events) were retrieved. Most of these cases were unsolicited reports; there were only 3 solicited reports. Eighty-two cases were HCP cases, and 5 originated from consumers. Most of these cases were non-serious (N= 53). The most frequently reported non-serious event was tinnitus, followed by transitory hearing impairment events.

Based on the data presented, deafness, hearing loss and tinnitus, have been adequately mentioned in section 4.8 of the proposed SmPC. Relevant information for patients treated with teicoplanin has been included in section 4.4 under the heading “Ototoxicity” for better readability. During long term treatment of concomitant or sequential treatment with teicoplanin and other potentially ototoxic and/or nephrotoxic medicinal products, monitoring of auditory function, liver and kidney function tests and regular haematology testing is recommended.

Superinfection

Precautionary measures regarding superinfection is not found in the SmPCs for Czech Republic and Spain. Superinfection has been included as a warning and also in section 4.8 of the SmPC. It has been recommended in section 4.4 that in case of superinfection, appropriate measures should be taken.

Agranulocytosis

A cumulative search of the MAH’s database identified 48 cases that were included for the analysis that was performed on patients receiving recommended and greater than recommended daily doses. Relevant confounders were identified in more than 2/3 of the cases, and included concomitant medications (eg, antibiotics or furosemide) and medical history/intercurrent conditions (eg, severe MRSA infection, septicaemia, blood dyscrasia, osteitis, severe decompensated state), or a combination of both.

Cases with supratherapeutic doses of teicoplanin were compared to cases with recommended daily doses teicoplanin therapy. No apparent difference between groups was identified in terms of time-to-event onset, severity of the outcome and time to recovery. There were no cases reporting fatal outcome associated with agranulocytosis. Overall, based on this analysis of agranulocytosis cases, the MAH’s argument that an inclusion of a warning in section 4.4 is not required was supported by the CHMP.

2.2.3.5 Section 4.5- Interaction with other medicinal products and other forms of interaction

In some local SmPCs (Austria, Belgium, Germany, Hungary, Ireland, Malta, Poland, Portugal, Romania, Slovenia, UK) it is mentioned that no interactions have been observed in clinical trials, where teicoplanin has been administered in combination with various medicinal products, such as other antibiotics, antihypertensives, cardiotropic and antidiabetic agents, without evidence of adverse

reactions. Some SmPCs (Belgium, Hungary, Ireland, Malta, Poland, Portugal, Romania, Slovenia and UK) also indicate that "Animal studies have revealed that there is no interaction with diazepam, thiopental, morphine, neuromuscular blocking agents and halothane". The lack of interaction between teicoplanin and other antibiotics, antihypertensives, cardiotropic, antidiabetic agents and anaesthetic agents has been included in the proposed harmonised SmPC.

No pharmacokinetic drug-drug interaction with teicoplanin has been carried out by the MAH, and no published data have been retrieved from the literature. A comprehensive literature search on drug interactions with teicoplanin was undertaken by global pharmacovigilance. This search was cumulative (up to 8-Aug-2012) and used Medline, Embase, Trial Trove and ClinicalTrials.gov databases. A statement regarding the absence of specific interaction studies has been added to the SmPC by the MAH and agreed by the CHMP.

Regarding interactions with teicoplanin, it is known that due to the potential for increased adverse effects, teicoplanin should be administered with caution in patients receiving concurrent nephrotoxic or ototoxic drugs, such as aminoglycosides, amphotericin B, ciclosporin, and furosemide. This information has been proposed by the MAH in the harmonised SmPC and was considered to be acceptable by the CHMP.

2.2.3.6 Section 4.6 – Fertility, pregnancy and lactation

The pregnancy statements that appear in the national SmPCs are similar to each other (although the actual wording differs in some instances), and suggest that there is limited human data. Reproductive toxicity was observed in animal studies at high doses, although there are major discrepancies between member states with regards to the information on reproductive studies in animals. Additional wording from the CSP (which was missing from some of the SmPCs), to indicate the nature of these observed effects has now been included in the MAH's proposal and is considered to be acceptable by the CHMP.

With the exception of Belgium, the information with respect to excretion into maternal milk is the same; however the recommendations during lactation differ. The applicant has not provided data to demonstrate a lack of effect on breast-fed newborns or infants; hence the sentence "No effects on the breastfed newborns/infants are anticipated since teicoplanin is not orally absorbed" has been deleted. The MAH has aligned the text so that it is in line with the CSP and the CHMP Guideline on risk assessment of medicinal products on human reproduction and lactation: From Data to labelling (EMEA/CHMP/203927/2005). The proposed wording was considered to be acceptable by the CHMP.

In accordance with the CHMP guideline and the SmPC Guideline, the applicant has also inserted information with regard to fertility, which was considered to be acceptable by the CHMP.

2.2.3.7 Section 4.7 - Effects on ability to drive and use machines

Bulgaria, Finland, Ireland, Italy, Malta, The Netherlands, Poland, Slovakia, Sweden and UK have exactly the same wording as the CSP. In Austria, Belgium, Denmark, France, Germany and Hungary the wording differs slightly but the same message is conveyed.

The wording of the CSP agreed during the PSUR work-sharing procedure (number GR/H/PSUR/0001/001) was considered to be acceptable by the CHMP.

2.2.3.8 Section 4.8 - Undesirable effects

Overall, the undesirable effects listed in the CSP agreed during the PSUR work-sharing procedure number GR/H/PSUR/0001/001 have been included in section 4.8 of the proposed harmonised SmPC using the MedDRA Preferred Terms (PTs) and classified by System Organ Class (SOC).

The frequencies of all listed adverse reactions have been calculated using data from in-house clinical trials results used for the original submission, and these were incorporated into the CSP during the

PSUR work-sharing procedure number GR/H/PSUR/0001/001, which was accepted by the member states. The proposed harmonised SmPC reflecting the changes was considered to be acceptable by the CHMP.

Seizures

Based on the cumulative analysis from the pharmacovigilance database and literature review, the cumulative weighted evidence is sufficient for a causal association between teicoplanin and convulsions. Consequently, the MAH proposed to maintain "Seizures" in section 4.8 of the SmPC.

Hepatotoxicity

The current CSP states "Transaminases abnormal (transient abnormality of transaminases), blood alkaline phosphatase abnormal (transient abnormality of alkaline phosphatase), blood creatinine increased (transient rise of serum creatinine)" under the SOC "Investigations". The conclusion of this analysis stated that the vast majority of cases either represented listed events, lacked information or were confounded by the presence of other disease states or medications. Therefore, the MAH proposes to keep the harmonized SmPC in line with the CSP and to continue monitoring this event.

The MAH has clarified that the review on cases of hepatotoxicity also included an analysis of hepatic events in the context of hypersensitivity reactions. It has been reported that teicoplanin may induce hepatitis as part of a hypersensitivity reaction[7] and the publication relating to this was cited in the analysis of the Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms (DRESS) syndrome reviewed during the PSUR Work-Sharing procedure. Of the 38 cumulative DRESS syndrome cases, confounding by concomitant therapy was present in all of these cases, mainly represented by vancomycin (27 cases), which usually preceded teicoplanin therapy, and also with other antibiotics. Cross-sensitivity between vancomycin and teicoplanin has been established and reflected in section 4.4 of the proposed SmPC for teicoplanin.

Purpura, hepatitis, paraesthesia, extrapyramidal syndrome and presence of anti-factor VII antibodies

The MAH has provided all available data from pre- and post-authorisation clinical and epidemiologic trials for purpura, hepatitis, paraesthesia, extrapyramidal syndrome and presence of anti-factor VII antibodies with bleeding. Based on the provided data there is currently no or not sufficient evidence to specifically label or monitor "purpura", "hepatitis", "Paraesthesia", "Extrapyramidal Syndrome", and "Anti-factor VII antibodies".

Loading dose

The effect of the higher loading dose (as proposed in section 4.2) on the possible occurrence of adverse drug reactions has also been addressed by the MAH. As stated by the MAH, literature articles on randomized controlled trials involving higher loading or maintenance doses of teicoplanin do not properly address the safety profile of a higher teicoplanin dosage, and in addition, no safety profile comparison with lower dosage is provided.

Safety data available for the loading dose of 12mg/kg bid (24mg/kg/day) that has now been recommended in case of severe infection is very limited: 40 patients with 24-36 mg/kg per day within the retrospective study by Matsumoto et al. (2010)[8] and 10 patients in the retrospective controlled

[7] Hsiao, S.-H., Chen, H.-H., Chou, C.-H., Lin, W.-L., Liu Yeh, P.-Y. and Wu, T.-J. (2010), Teicoplanin-induced hypersensitivity syndrome with a preceding vancomycin-induced neutropenia: a case report and literature review. Journal of Clinical Pharmacy and Therapeutics, 35: 729–732.

[8] Kazuaki Matsumoto, Naoko Kanazawa, Kazuro Ikawa, Tomohide Fukamizu, Akari Shigemi, Keiko Yaji, Yoshihiro Shimodozono, Norifumi Morikawa, Yasuo Takeda, and Katsushi Yamada. Determination of teicoplanin trough

trial by Fortun *et al*. (2001)[9]. Since this loading dose of 12mg/kg bid (24mg/kg/day) is not well established, a clear statement in section 4.8 has been included in the SmPC that patients should be especially monitored for adverse reactions when higher dosages of Targocid 12mg/kg bid (24mg/kg/day) are administered. Additionally, as mentioned above, the MAH has been requested to perform an appropriate PASS to evaluate the safety of this higher dosage.

Thrombocytosis

In Spain, thrombocytosis has been mentioned in the SmPC since the initial approval in 1991. It is also mentioned in the SmPCs in Denmark, Norway, Romania, Slovenia and Sweden.

The MAH has reviewed and submitted the global pharmacovigilance data, the cumulative medical/scientific literature, the registration and amendment dossiers, and the information associated with the SmPCs including thrombocytosis. Three cases of thrombocytoses and 2 cases of increased platelet count were found in the Sanofi global pharmacovigilance database over the 25 year time span from November 1986 to November 2011. In summary, 4 cases either lacked or had a questionable temporal association, and in 1 case there was an alternative explanation for the event (concomitant therapy). Overall, the MAH's argument that the data are not sufficient for a causal assessment was endorsed by the CHMP.

2.2.3.9 Section 4.9 – Overdose

Some discrepancies result from the fact that some countries have not yet updated their labelling in accordance to the CSP agreed during the PSUR work sharing procedure number GR/H/PSUR/0001/001, or that specific information has been maintained in the local labels by the National Competent Authorities (NCA) such as thrombocytopenia, leukopenia, agranulocytosis, hypersensitivity reactions and renal failure in the context of overdose.

No new specific reactions due to teicoplanin overdose in the adult population have been identified. In the paediatric population, an adverse reaction was not reported in most cases of teicoplanin overdose; agitation and vomiting are confounded by concomitant treatments or clinical situation.

The wording of the CSP agreed during the PSUR work-sharing procedure (number GR/H/PSUR/0001/001) was considered to be acceptable by the CHMP.

2.2.3.10 Section 5.1 - Pharmacodynamic properties

The antibacterial spectrum has been updated in accordance with the CHMP Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CHMP/EWP/588/95 rev 2).

In the current version of EUCAST MIC breakpoints, the resistance breakpoint for Staphylococcus aureus has been reduced to >2 mg/ml to avoid reporting of glycopeptide intermediate resistant Staphylococcus aureus (GISA) isolates, as serious infections with GISA isolates are not treatable with increased doses of vancomycin or teicoplanin.

Regarding Enterococcus spp., the resistance breakpoint for teicoplanin has been reduced to >2 mg/ml to avoid erroneous reporting of isolates with Van-A-mediated resistance. For coagulase-negative staphylococci (CoNS), the resistance breakpoint is >4 mg/ml.

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concentration target and appropriate total dose during the first 3 days: a retrospective study in patients with MRSA infections. J Inf Chemother (2010) 16:193-9

[9] Fortun Jesus, Navas Enrique, Matinez-Beltran Jesus, J. Perez-Molina, Pilar Martin-Davila, Antonio Guerrero, and Santiago Moreno. Short-Course Therapy for Right-Side Endocarditis Due to Staphylococcus aureus in Drug Abusers: The study EG-85-3 Cloxacillin versus Glycopeptides in Combination with Gentamicin. Clinical Infectious Diseases 2001;33:120-5

The microbiological spectrum of teicoplanin covers staphylococci including Staphylococcus aureus susceptible or resistant to methicillin, Streptococcus pneumoniae and other streptococci mainly including Streptococcus pyogenes, streptococci in the Viridans group and Enterococcus faecalis.

Recent time-kill studies confirm that *in vitro* bactericidal activity of teicoplanin is optimally tested according to CLSI guidelines, with tolerance defined at 24 hours.

2.2.3.11 Section 5.2 - Pharmacokinetic properties

There are some discrepancies in the sections “absorption” and “distribution” into tissues and body fluid, due to missing or more detailed information within the local SmPCs. Information on the bioavailability after IM administration is not available in some member states. No discrepancies were found in the subsection “Biotransformation”. The “Elimination” subsection is not always documented with the elimination pharmacokinetic parameters in most member states. Some pharmacokinetic information for the paediatric population is included in some member states.

The harmonization of the pharmacokinetic section in the teicoplanin SmPC is based on the data first provided in the initial MAA, and more recent data retrieved from a literature research. The general format proposed by the MAH is in accordance with the EU guideline on the SmPC and was therefore considered to be acceptable by the CHMP. Linearity of the pharmacokinetics as well as a statement addressing special populations has also been included, in line with the above mentioned EU guideline.

Absorption

By IV administration, Tmax of an active substance always occurs at end of infusion. The pharmacokinetic parameters i.e. Cmax and Ctrough, of teicoplanin were extracted from literature data when dosing regimens used corresponded to those specified in the proposed harmonized teicoplanin SmPC section 4.2:

- loading dose: 6 mg/kg or 12 mg/kg every 12 hours for 3 to 5 administrations
- maintenance dose 6 mg/kg or 12 mg/kg once daily

As no literature data are available for the IM route, the results of the pharmacokinetic study of teicoplanin after repeated IM injections was used to document Cmax by this route.

Distribution

The study on distribution of teicoplanin in peritoneal fluid was performed in 34 patients undergoing abdominal surgery and receiving a single IV dose of 400 mg at different times varying from 0.5 to 17 hours preoperatively. For both serum and peritoneal fluid maximum concentrations of teicoplanin were observed at 0.5h, then concentrations decreased in the same way until 17 hours.

Elimination

The elimination half-life was not calculated in study EG-85-3 as the teicoplanin elimination half-life from serum is very long (ranging from 100 to 170h), and the short period of this study (17h) did not allow any relevant calculation of the teicoplanin elimination half-life in serum and peritoneal fluid. As the peritoneal concentrations parallel those of serum over the study period, it could be assumed that teicoplanin elimination from peritoneal fluid occurs at the same rate as from serum without any accumulation. A statement regarding the elimination of teicoplanin from peritoneal fluid has been inserted in section 5.2.

The linearity of the teicoplanin pharmacokinetics in the dose range 2 to 25 mg/kg has been demonstrated and a statement has been added in the section 5.2 of the SmPC.

2.2.3.12 Section 5.3 - Preclinical safety data

There are differences in the SmPCs of the member states with regard to the wording on acute and chronic studies, reproductive toxicity, mutagenicity and teratogenicity and local tolerability.

The proposed harmonised SmPC has been updated with additional information on target organs and reproductive toxicity. The preclinical safety data reported support these proposed amendments and are provided within the expert report on the toxicological and pharmacological documentation. Further amendments to the wording of the reproductive toxicity section have been included as requested by the CHMP.

2.2.3.13 Package Leaflet (PL)

Following all the changes in the SPC there are several corresponding changes to the Package Leaflet. A Readability Testing was performed and submitted during the referral procedure. The final PL wording was agreed by the CHMP.

2.3. Risk minimisation activities

Post-authorisation safety study (PASS)

Since safety data for the loading dose of 12mg/kg bid (24mg/kg/day) is limited, the MAH has been requested by the CHMP to conduct a post-authorisation safety study (PASS) to evaluate the safety of the higher loading dose of Targocid 12mg/kg bid (24mg/kg/day). This PASS is imposed as a legally binding measure that is a condition to the Marketing Authorisation.

The MAH shall submit the study protocol for assessment to the European Medicines Agency and to the PRAC in line with requirements of GVP module VIII (Addendum I). The protocols, abstracts and final study reports shall be submitted in the format set out in Annex III of the Commission Implementing Regulation (EC) No 520/2012. The study protocol shall be entered in the EU electronic register of post-authorisation studies (EU PAS Register) before the start of data collection.

The study protocol of this non-interventional PASS shall be submitted within 2 months of the Commission Decision.

2.4. Risk management plan (RMP)

The CHMP has requested the MAH to submit a RMP within 6 months of the Commission Decision to adequately address the important potential risks, in particular, the increased frequency of nephrotoxicity and other serious reactions with loading doses of Targocid 12mg/kg bid (24mg/kg/day). The PASS protocol should also be included in the RMP.

2.5. Recommendation

The indication for the prophylactic use of teicoplanin in orthopaedic surgery was not considered to be acceptable by the CHMP. The open-labelled comparative studies that were submitted in support of this indication were not sufficiently robust, as they did not demonstrate that teicoplanin was better than the comparators.

A clear warning has been included in the SmPC that patients should be especially monitored for adverse reactions when the higher dosage of 12mg/kg bid (24mg/kg/day) is administered.

Since safety data for the loading dose of Targocid 12mg/kg bid (24mg/kg/day) is limited, the MAH has agreed to the request made by the CHMP to perform an appropriate post authorisation safety study (PASS) to evaluate the safety of the higher loading dose of 12mg/kg bid(24mg/kg/day).

The CHMP has requested the MAH to submit a RMP (in which the PASS protocol will be included) to adequately address the important potential risks, in particular, the increased frequency of nephrotoxicity and other serious reactions with loading doses of Targocid 12mg/kg bid (24mg/kg/day). The PASS protocol shall be included in the RMP.

The MAH is expected to submit the PASS protocol within 2 months as of the Commission decision, and the RMP within 6 months as of Commission decision.

2.6. Conclusions

In conclusion, based on the assessment of the proposals submitted by the MAH and the discussions of the Committee, the CHMP adopted the harmonised product information consisting of the summary of product characteristics (SmPC), labelling and package leaflets, for Targocid and associated names.

A harmonised Module 3 was also adopted.

Based on the above, the CHMP considers the benefit/risk ratio of Targocid and associated names to be favourable and the harmonised Product Information documents to be approvable.

Whereas

- The Committee considered the referral under Article 30 of Directive 2001/83/EC
- The Committee considered the identified divergences in the product information for Targocid and associated names with respect to the therapeutic indications, posology and method of administration sections, contraindications and special warnings and precautions for use, as well as the remaining sections of the SmPC.
- The Committee reviewed the available data on submitted by the MAH from the existing clinical studies, the pharmacovigilance data and the published literature justifying the proposed harmonisation of the SmPC.
- The Committee agreed the harmonisation of the summary of product characteristic, labelling and package leaflet proposed by the marketing authorisation holder.

the CHMP has recommended the variation to the terms of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Targocid and associated names (see Annex I).

In addition, the CHMP has recommended conditions to the Marketing Authorisation which are set out in Annex IV of the CHMP opinion.