Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation

Scientific conclusions

Overall summary of the scientific evaluation of Targocid and associated names (see Annex I)

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.

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.

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.

- **Quality issues**

The MAH took the opportunity to harmonise the Quality dossier for Targocid and associated names as part of the 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.

Information on the active substance was submitted in an ASMF. Detailed information on the starting materials, fermentation and purification process was provided and found acceptable.

Harmonisation of the active substance specification was needed as tighter limits for the individual subcomponents were approved in some Member States, compared to the current Ph. Eur. monograph. 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. It can be concluded that batch results prove good consistency of the manufacturing process.

A valid TSE certificate was provided for the active substance.

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The finished product 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 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).

The shelf-life of the product is supported by relevant stability data.

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that these products should have a satisfactory and uniform performance.

- **Clinical issues**

Section 4.1 – Therapeutic Indications

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.

The efficacy of teicoplanin in the treatment of Gram-positive infections has been investigated in a number of clinical studies that were submitted in the initial authorisation along with literature references. The clinical studies included two open-label non-comparative therapeutic studies; the European Multicentre Study (EG-87-42) and the US Open Multicentre Study (N-86-04) and a review of the comparative studies conducted with teicoplanin (EG-87-35). Most of the patients included in study EG-87-42 (which was the larger of the two non-comparative 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.

Treatment of infections caused by Gram-positive microorganisms

The following infections caused by Gram-positive microorganisms were discussed by the CHMP:

- Skin and soft tissue infections (SSTI)

The clinical and bacteriological efficacy of teicoplanin was shown in SSTIs (37.4% of all infection sites) in Study EG-87-42 (European Multicentre Study).

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 clinical and bacteriological efficacy of teicoplanin was shown in both the European Multicentre Study and in 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

In Study EG-87-42, 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%. Other studies were also discussed by the MAH.

The results from the various studies discussed by the MAH 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 4.4 commenting on the limited spectrum of antibacterial use and its rational use has been included.

- Bacteraemia/ Septicaemia / Sepsis

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)

In Study EG-87-42 (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.

- Infective endocarditis

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 (EG-87-42 and N-86-04) conducted in support of the initial marketing authorisation. In study EG-87-42, the clinical outcome for endocarditis was 83% (excluding patients considered as non-evaluable).

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)

There is evidence to suggest that teicoplanin is effective in this indication. Indeed, in a Cochrane meta-analysis of randomised controlled trials (RCT) in adults and children with CAPD-associated peritonitis, although the primary response and relapse rates did not differ between intraperitoneal (IP) glycopeptide-based regimens compared to first generation cephalosporin regimens, 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)[1]. 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.

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.

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

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

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

pseudomembranous colitis (PMC) caused by *C. difficile*. 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 in study DRC342-DLI073. 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 Member States. 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. 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.

Section 4.2 - Posology and method of administration

Posology

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. 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[2] 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 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 12mg/kg bid (24mg/kg/day).

[2] 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.

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 4 months should be avoided.

Method of administration

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.

Paediatric population

In the four published studies of the initial dossier, the 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 [3]and Reed in 1997[4], 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.

Section 4.3 - Contraindications

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

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, infusion related reactions (Red Man Syndrome), severe bullous reactions (including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)), warning concerning the possible adverse reactions with the higher loading dose of 12mg/kg bid

[3] 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.

[4] Reed MD, Yamashita TS, Myers CM, et al. The pharmacokinetics of teicoplanin in infants and children. J Antimicrob Chemother 1997 ; 39: 789-96.

(24mg/kg/day), thrombocytopenia, nephrotoxicity, ototoxicity and superinfection. 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 was proposed by the MAH, and accepted by the CHMP. 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".

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

Section 4.6 – Fertility, pregnancy and lactation
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 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. In accordance with the CHMP guideline and the SmPC Guideline, the applicant has also inserted information with regard to fertility.

The proposed wording was considered to be acceptable by the CHMP.

Section 4.7 - Effects on ability to drive and use machines
The wording of the CSP agreed during the PSUR work-sharing procedure (GR/H/PSUR/0001/001) was considered to be acceptable by the CHMP.

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.

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. 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 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.

Section 4.9 – 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 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.

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.

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.

Section 5.2 - Pharmacokinetic properties

The harmonization of the pharmacokinetic section in the teicoplanin SmPC is based on the data first provided in the initial marketing authorisation application, 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 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.

Section 5.3 - Preclinical safety data

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.

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.

Risk minimisation activities

Post-authorisation safety study (PASS)

Since safety data for the loading dose of12mg/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 12mg/kg bid. This PASS is imposed as 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 as of the Commission Decision.

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 12mg/kg bid (24mg/kg/day). The PASS protocol should also be included in the RMP.

Grounds for the variation to the terms of the marketing authorisation

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.