27 February 2020
EMA/140293/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tigecycline Accord

International non-proprietary name: tigecycline

Procedure No. EMEA/H/C/005114/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CRS	Chemical Reference Substance (official standard)
DSC	Differential Scanning Calorimetry
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FPen	Penetration factor (proportion of the population being treated daily
GC	Gas Chromatography
GCP	Good Clinical Practice
GC-MS	Gas chromatography mass spectrometry
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
KF	Karl Fischer titration
LC-MS	Liquid chromatography mass spectrometry
LDPE	Low Density Polyethylene
MAA	Marketing authorisation application
NMR	Nuclear Magnetic Resonance
PBTs	Persistent, bioaccumulative and toxic substances
PEC	Predicted Environmental Concentration
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PopPK	Population PK
RH	Relative Humidity
RMP	Reference Medicinal Product
SmPC	Summary of Product Characteristics
USP	United States Pharmacopoeia
USNF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 30 July 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Tigecycline Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 June 2018.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

"Tygecycline Accord is indicated in adults and in children from the age of eight years for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated skin and soft tissue infections (cSSTI), excluding diabetic foot infections (see section 4.4)
- Complicated intra-abdominal infections (cIAI)

Tygecycline Accord should be used only in situations where other alternative antibiotics are not suitable (see sections 4.4, 4.8 and 5.1).

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

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a non-clinical overview on the pharmacology, pharmacokinetics and toxicology and a clinical overview.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Tygacil
- Marketing authorisation holder: Pfizer Europe MA EEIG
- Date of authorisation: 24-04-2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/336/001

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Tygacil
- Marketing authorisation holder: Pfizer Europe MA EEIG
- Date of authorisation: 24-04-2006
- Marketing authorisation granted by:
  - Union

- Marketing authorisation number: EU/1/06/336/001

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Milena Stain

The application was received by the EMA on	30 July 2018
The procedure started on	16 August 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	5 November 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	16 November 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	13 December 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	28 March 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	06 May 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The CHMP agreed on a 1st list of outstanding issues in writing to be sent to the applicant on	29 May 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 August 2019
The Rapporteurs circulated the Joint Assessment Report on the	04 September 2019

responses to the List of Outstanding Issues to all CHMP members on	
The CHMP agreed on 2nd list of outstanding issues in writing to be sent to the applicant on	19 September 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	08 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	26 November 2019
The CHMP agreed on 3rd list of outstanding issues in writing to be sent to the applicant on	12 December 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 February 2010
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tigecycline Accord on	27 February 2020

2. Scientific discussion

2.1. Introduction

Tigecycline is a member of tetracycline class of antibiotics that prevents bacterial growth by inhibiting protein synthesis. Tigecycline inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. Tetracycline antibiotics are active against a broad spectrum of bacteria. They have displayed in vitro activity against the most common causative Gram-positive, Gram-negative and anaerobic pathogens. In addition, tigecycline has demonstrated activity against drug-resistant pathogens such as methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, and organisms producing extended-spectrum beta-lactamases (such as Escherichia coli and Klebsiella pneumoniae). Tigecycline is a third-generation tetracycline, which has a modified structure for dealing with the known resistance mechanisms of bacteria.

This application concerns a generic application according to article 10(1) for Tigecycline Accord, powder for solution for infusion, 50 mg/vial. The reference product is the centrally authorised medicinal product Tygacil, which has been authorised in the EU since April 2006.

This product is exempt from conducting a bioequivalence study, in accordance with Appendix II of the current Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). The selected excipients are amongst the excipients listed in the innovator product Tygacil, except for lactose monohydrate. Maltose monohydrate is used in the proposed formulation in place of lactose monohydrate present in the innovator product Tygacil; both have similar physical properties. Tigecycline Accord is intended for the same indication, using the same dosage regimen and route of administration as Tygacil.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder for solution for infusion containing 50 mg of tigecycline. After reconstitution, 1 ml contains 10 mg of tigecycline.

Other ingredients are maltose monohydrate, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

The product is available in 10 ml Type 1 clear glass vials fitted with grey bromobutyl rubber stopper and flip-off aluminium seal as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of tigecycline is (4*S*, 4*aS* 5*aR*, 12*aS*)-4, 7-bis(dimethylamino)-9-[[[(1,1-dimethylethyl)amino] Acetyl]amino]-1,4,4a,5,5a,6,11,12*a*-octahydro-3,10,12,12 a tetrahydroxy-1,11-dioxo-2- naphthacenecarboxamide corresponding to the molecular formula $C_{29}H_{39}N_5O_8$. It has a molecular weight of 585.65 g/mol and the following structure:

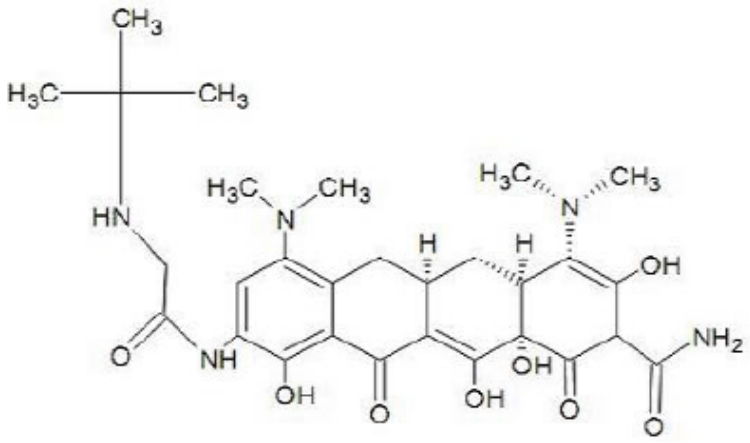

Figure 1: active substance structure

The chemical structure of the active substance was elucidated by a combination of IR spectroscopy, UV spectrophotometry, Nuclear Magnetic Resonance (NMR) and Liquid chromatography–mass spectrometry (LC-MS). The solid-state properties of the active substance were measured by Differential scanning calorimetry (DSC) and X-Ray Diffraction.

The active substance is an orange, hygroscopic, powder. It is freely soluble in water, slightly soluble in anhydrous ethanol and in heptane.

Tigecycline exhibits stereoisomerism due to the presence of four chiral centres. Chiral centres present in the active substance are derived from the starting material (minocycline HCl). Stereoisomeric purity is routinely controlled in the active substance specifications, as per Ph. Eur.

Tigecycline is known to show polymorphism. Results from three consecutive active substance batches confirm that the described manufacturing process consistently gives the active substance of amorphous form. Since the finished product needs to be reconstituted prior to administration as solution for infusion, polymorphism is not considered a critical aspect for finished product performance.

There is a monograph of tigecycline in the European Pharmacopoeia and the active substance specifications comply with the Ph. Eur.; however, the manufacturer of the active substance has not provided a CEP for the active substance.

Manufacture, characterisation and process controls

The active substance is obtained from a single supplier. Initially it was proposed to source the active substance from two different sources, however one of the proposed sources was withdrawn during the procedure. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is synthesised in six main steps using well defined starting materials with acceptable specifications.

During the procedure, the CHMP requested additional information regarding the justification of the chosen starting material. Following the provided justifications, the initially proposed starting material was accepted.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Primary packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance (Ph. Eur.), solubility (Ph. Eur.), identification (IR), water content (KF), pH (Ph. Eur.), sulfated ash (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (GC), bacterial endotoxins (Ph. Eur.), microbial examination (Ph. Eur.), and genotoxic impurities (GC-MS).

The provided specification complies with the Ph. Eur. monograph for tigecycline. The following parameters are tested additionally to those referenced in Ph. Eur.: residual solvents, bacterial endotoxins, microbiological quality (the proposed limits are in-line with Ph. Eur. 5.1.4) and genotoxic impurities.

Ph. Eur. impurities A, B and C are specified with limits that comply with the limits referenced in the Ph. Eur. monograph for Tigecycline (2825). Ph. Eur. impurity D is controlled as unspecified impurity, again in-line with Ph. Eur. monograph 2825.

A discussion of genotoxic impurities according to ICH M7 was presented and found acceptable.

Nitrosamines N-nitroso dimethyl amine and N-nitroso diethyl amine have been identified as potentially formed impurities of the active substance. Confirmatory testing on three production scale batches using appropriately validated and sensitive methods has shown that no nitrosamines were detected. The applied method is considered capable to guarantee sufficiently low levels of nitrosamines, which are routinely tested in active substance specifications.

Batch data demonstrating absence of heavy metal catalyst residues in the active substance have been provided.

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

Batch analysis data on three consecutive commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from six batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 12 months under long term conditions (2°C - 8°C) and from six batches for up to 6 months under accelerated conditions (25°C ± 2°C / 60% ± 5% RH) according to the ICH guidelines were provided. All tested parameters were within the specifications.

The following parameters were tested*:* description, water content, pH, specific optical rotation, related substances and assay. Stability testing has been performed using USP methods. Equivalence data for batches tested using USP and Ph. Eur. methods are presented and are considered acceptable and comparable irrespective of whether testing was performed according to USP or Ph. Eur. This supports the conclusion that stability data derived from testing using USP methods are representative for testing according to Ph. Eur. monograph.

Results on stressed conditions: oxidation, alkaline medium, acidic medium, 60°C temperature, 30°C temperature and 75% RH and exposure to UV light were also provided on one batch.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period when stored in an airtight container and protected from light.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as powder for solution for infusion containing 50 mg of tigecycline, maltose monohydrate, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment). After reconstitution, 1 ml contains 10 mg of tigecycline. Detailed composition of the finished product is provided in Table 2. The medicinal product is supplied in vials as a sterile lyophilized powder or cake.

The aim of the pharmaceutical development was to develop a stable generic of the reference medicinal product (RMP) Tygacil. The proposed product has the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form as the RMP. Maltose monohydrate is used in the proposed formulation instead of lactose monohydrate in the RMP, which is sufficiently justified. The excipient maltose monohydrate is used in place of lactose monohydrate used in the RMP as both are having similar physical properties. Maltose monohydrate and lactose monohydrate both are disaccharide carbohydrates. Based on provided references, maltose is generally well tolerated, and it has no clinically significant interactions with other drugs. Based on the provided discussion it is concluded that metabolic and disposition pathway of tigecycline and maltose is sufficiently different rendering interference of maltose not likely.

All excipients are well known pharmaceutical ingredients and their quality is compliant with compendial monographs. The given specifications are considered justified and adequate. No description and validation of method is required. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Similarity to the RMP is shown by the Applicant in terms of composition, impurity parameters, X-ray diffractogram, pH and osmolality (on reconstituted and diluted product), and other chemical parameters.

The proposed overfill in order to achieve the same final concentration of the generic- and the RMP is fully acceptable and the parameters, which might affect the physicochemical properties of the finished product, have been sufficiently discussed.

Manufacturing process development is covered by 13 studies and compatibility studies are provided. The sterilisation method is fully justified following the relevant guidance. Bulk holding time has been justified.

Compatibility, reconstitution and dilution stability studies were performed. During the procedure the CHMP requested that more information is provided regarding the in-use stability data. Following the submission of requested information, the in-use stability as described in the SmPC has been found acceptable. A stability of diluted solutions for 24 hours at 20-25°C and 48 hours at 2-8°C and of reconstituted product for 6 h at 20-25°C is acceptable.

The primary packaging is a clear glass vial stoppered with rubber stopper and sealed with an aluminium flip-off seal. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The provided leachable study was considered acceptable. Microbiological attributes are sufficiently covered for development.

During the procedure, the risk of formation of nitrosamine impurities was addressed for the active substance. It is recommended that an updated risk evaluation on the potential presence of nitrosamine impurities is performed also for the Tigecycline Accord finished product within six months of the marketing authorisation. In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within a year after the marketing authorisation or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

Manufacture of the product and process controls

The manufacturing process consists of nine main steps: manufacturing of the bulk solution, pre-filtration, vial preparation (washing/depyrogenation), rubber stopper preparation (sterilisation), aluminium seal preparation (sterilisation), filling equipment preparation (sterilisation), filling and half stoppering, lyophilisation and sealing, and finally inspection, labelling and packaging. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on three commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (in-house), identification (HPLC, UV), reconstitution time (in-house), pH of the reconstituted solution (Ph. Eur.), clarity of reconstituted solution (Ph. Eur.), colour of reconstituted solution (Ph. Eur.), visible particles of reconstituted solution (Ph. Eur.), water (KF), uniformity of dosage units (Ph. Eur.), organic impurities (HPLC), assay (HPLC), particulate contamination (sub-visible) (Ph. Eur.), bacterial endotoxins (Ph. Eur.), and sterility (Ph. Eur.).

Specification parameters are considered appropriate for the dosage form. The finished product is released on the market based on the release specifications, through traditional final product release testing.

For impurities, an identification and qualification threshold of ≤ 0.2% is applied. A discussion of the chosen limit of bacterial endotoxins in the context of the applied administration is provided and considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

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

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

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 18 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for: description, reconstitution time, pH of the reconstituted solution, clarity of reconstituted solution, colour of reconstituted solution, visible particles of reconstituted solution, water, organic impurities, assay, particulate contamination, bacterial endotoxins, and sterility. The analytical procedures used are stability indicating. No significant changes have been observed and results were found to comply with the specification limits at the applicable time points throughout the duration of the studies.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not photosensitive.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 6 hours at 20 - 25°C, for the diluted solution for 24 hours at 20 - 25°C and for 48 hours at 2 - 8°C. From a microbiological point of view, the 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 not be longer than the times stated above for the chemical and physical in-use stability.

Based on available stability data, the proposed shelf-life of 2 years as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

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

The assessment on nitrosoamine impurities in active substance is adequately described in dossier.

Nitrosamines N-nitroso dimethyl amine and N-nitroso diethyl amine have been identified as potentially formed impurities of the active substance. Confirmatory testing on three production scale batches using appropriately validated and sensitive methods has shown that no nitrosamines were detected. The applied method is considered capable to guarantee sufficiently low levels of nitrosamines, which are routinely tested in active substance specifications. It is recommended that an updated risk evaluation on the potential presence of nitrosamine impurities is performed also for the Tigecycline Accord finished product within six months of the marketing authorisation.

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

It is recommended that an updated risk evaluation on the potential presence of nitrosamine impurities in Tigecycline Accord finished product is conducted within six months of the marketing authorisation. In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within a year after the marketing authorisation or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Tigecycline Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the combined sales volumes for all tigecycline containing products and the exposure of the environment to the active substance.

2.3.3. Conclusion on the non-clinical aspects

The non-clinical sections of the SmPC are acceptable and in line with the reference product. The grounds for not providing new non-clinical data are adequately justified. The non-clinical overview on pharmacology, pharmacokinetics and toxicology submitted by the applicant for Tigecycline Accord 50 mg powder for solution for infusion is considered sufficient and the ERA is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is a centralised Marketing Authorisation Application under Article 10(1) of Directive 2001/83/EC for Tigecycline Accord 50 mg powder for solution for infusion, in the following indication:

Tigecycline Accord is indicated in adults and in children from the age of eight years for the treatment of the following infections (see sections 4.4 and 5.1):

- *Complicated skin and soft tissue infections (cSSTI), excluding diabetic foot infections (see section 4.4);*
- *Complicated intra-abdominal infections (cIAI).*

Tigecycline Accord should be used only in situations where other alternative antibiotics are not suitable (see sections 4.4, 4.8 and 5.1).

The reference product is Tygacil by Pfizer Limited, UK, authorised in EU since 2006. The Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) is relevant for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

Exemption

This medicinal product is a parenteral preparation; therefore, a bioequivalence study is not required according to appendix II of the current Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1).

Additionally, Tigecycline Accord contains the same active substance and applies for the same indications, pharmaceutical form, route of administration, and the same strength as the reference product Tygacil. The composition of Tigecycline Accord is the same as that of Tygacil with the exception that lactose is substituted with maltose in the proposed product. Changes in inactive ingredients (excipients) can be acceptable if it can be substantiated that these differences will not affect the *in vivo* behaviour of the proposed drug product. The applicant submitted a justification arguing that the difference in excipients will not affect the efficacy of the active substance. This is accepted as a satisfactory justification and no further studies are required.

2.4.2. Pharmacokinetics

No bioequivalence study was submitted to support this Marketing Authorisation Application and no such study is required according to appendix II to the Guideline on the Investigation of Bioequivalence as the test product is to be administrated as an aqueous intravenous solution containing the same active substance as the reference product. The test product contains the same excipients as the reference product except for the substitution of lactose monohydrate for maltose monohydrate.

Tigecycline Accord is considered to be essentially similar to Tygacil.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The submitted Clinical Overview is sufficient, as it contains an adequate review of published clinical data. Based on the appendix II of the current Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), a bioequivalent study is not required.

The test product contains the same excipients as the reference product except for the substitution of lactose monohydrate for maltose monohydrate. This difference of excipient is acceptable.

2.4.6. Conclusions on clinical aspects

From a clinical point of view, the application is approvable.

2.5. Risk management plan

Safety concerns

The safety profile of the product is aligned to the reference medicinal product.

Important identified risks	• Thrombocytopenia • Hepatotoxicity • Anaphylaxis/anaphylactoid skin reactions • Pancreatitis • Superinfection
Important potential risks	• QTc prolongation/Torsades de pointes • Clostridium difficile associated diarrhoea and pseudomembranous colitis • Lack of efficacy
Missing information	• Use in paediatric patients aged less than 8 years • Use in pregnant and breast-feeding women • Use in patients with neutropenia • Use in patients on immunosuppressant therapy

Pharmacovigilance plan

There are no ongoing or additional planned pharmacovigilance activities proposed. Having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product and no additional pharmacovigilance activities are necessary.

Risk minimisation measures

The safety information in the proposed product information is aligned to the reference medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Tygacil. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of tigecycline powder for solution for infusion. The reference product Tygacil is indicated in adults and in children from the age of eight years for the treatment of complicated skin and soft tissue infections (cSSTI), excluding diabetic foot infections, and of complicated intra-abdominal infections (cIAI), in situations where other alternative antibiotics are not suitable.

The product is a parenteral preparation and therefore, according to appendix II of the current Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), a bioequivalence study is not required. From a non-clinical and clinical point of view, the application is approvable.

A benefit/risk ratio comparable to that of the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tigecycline Accord is favourable in adults and in children from the age of eight years for the treatment of complicated skin and soft tissue infections (cSSTI), excluding diabetic foot infection, and of complicated intra-abdominal infections (cIAI), in situations where other alternative antibiotics are not suitable.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.