13 October 2016
EMA/CHMP/663395/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tigecycline Accord

International non-proprietary name: tigecycline

Procedure No. EMEA/H/C/004419/0000

Note

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

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LIST OF ABBREVIATIONS

AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BP	British Pharmacopoeia
CEP	Certificate of Suitability of the European Pharmacopoeia
CMS	Concerned Member State
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DMF	Drug Master File = Active Substance Master File
DP	Decentralised (Application) Procedure
IPC	In-process control
IR	Infrared
IU	International Units
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantification
LoQ	List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
PL	Patient Leaflet
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
UV	Ultraviolet
USP/NF	United States Pharmacopoeia/National Formulary
XRD	X-Ray Diffraction

* This is a general list of abbreviations. Not all abbreviations may be used.

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the generic application for Tigecycline Accord Powder for solution for infusion 50mg/vial indicated in adults and in children from the age of eight years for the treatment of the following infections:

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

Tigecycline should be used only in situations where other alternative antibiotics are not suitable.

is not approvable, since a major objection has been identified, which precludes a recommendation for marketing authorisation at the present time.

The major objection precluding a recommendation of marketing authorisation, pertains to the following principal deficiencies:

GMP non-compliance for the active substance manufacturing site has been identified by the European Medicines Agency Compliance and Inspection Service.

Proposal for questions to be posed to additional experts

N/A

- Proposal for inspection

GMP inspection(s)

Dossier provided in Module 3 is generally in accordance with the quality scientific guidelines, general Ph.Eur. requirements; therefore from the quality part there is no reason for the request for inspection action prior to authorisation.

Inspections of the drug substance manufacturing sites and /or the drug product manufacturing sites and /or the batch release sites are not considered necessary for the completion of the module 3 assessment, however GMP non-compliance for the active substance manufacturing site has been identified. For that reason the procedure is not approvable at the moment.

GCP inspection(s)

N/A

2. Executive summary

2.1. Problem statement

N/A– generic application

2.2. About the product

This application for a marketing authorisation concerns a generic application of a Centrally Authorised Medicinal Product according to article 10(1) for Tigecycline Accord Powder for solution for infusion

50mg/vial. The reference product is Tygacil which has been authorised in the EU since April 2006 through centralised procedure by Pfizer Limited, United Kingdom.

This product is exempted from the bioequivalence study in accordance with Annex II to the Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev.1. It is intended to be used for the same indication, in the same dosage regimen and route(s) of administration as Tygacil.

This medicinal product is supplied in vials as a sterile lyophilized powder or cake containing 50 mg/vial of Tigecycline.

Tigecycline is a member of tetracycline class of antibiotics that prevents bacterial growth by inhibiting the protein synthesis. The tetracycline antibiotics are active against a broad spectrum of bacteria. They have displayed an activity *in vitro* 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, a glycylcycline antibiotic, 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. Tigecycline is a part of the third generation of tetracyclines which has modified structure for dealing with the known resistance mechanisms of bacteria.

Proposed indication

Tigecycline Accord is indicated in adults and in children from the age of eight years for the treatment of the following infections:

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

Tigecycline should be used only in situations where other alternative antibiotics are not suitable.

Posology

Adults

The recommended dose for adults is an initial dose of 100 mg followed by 50 mg every 12 hours for 5 to 14 days.

The duration of therapy should be guided by the severity, site of the infection, and the patient's clinical response.

Hepatic impairment

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B).

In patients (including paediatrics) with severe hepatic impairment (Child Pugh C), the dose of Tigecycline Accord should be reduced by 50 %. Adult dose should be reduced to 25 mg every 12 hours following the 100 mg loading dose. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response

Renal impairment

No dosage adjustment is necessary in patients with renal impairment or in patients undergoing haemodialysis

Elderly

No dosage adjustment is necessary in elderly patients

Paediatric population

Tigecycline Accord is only to be used to treat patients aged 8 years and older after consultation with a physician with appropriate experience in the management of infectious diseases.

Children aged 8 to <12 years: 1.2 mg/kg of tigecycline every 12 hours intravenously to a maximum dose of 50 mg every 12 hours for 5 to 14 days.

Adolescents aged 12 to <18 years: 50 mg of tigecycline every 12 hours for 5 to 14 days.

Children under 8 years of age:

The safety and efficacy of Tygacil in children under 8 years of age have not been established. No data are available. Tygacil should not be used in children aged under 8 years because of teeth discolouration.

Method of administration:

Tigecycline Accord is administered only by intravenous infusion over 30 to 60 minutes. Tigecycline should be preferably administered over a 60-minute length of infusion in paediatric patients.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The CHMP Guidelines were followed.

The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Names, addresses and responsibility of each manufacturer are provided. Some comments to the GMP certificates have been raised from inspection section. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites; with minor concerns remaining. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites; with minor concerns remaining. Regarding the statement on GMP for the active substance a declaration is provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU, however the declaration is not acceptable.

Inspections of the drug substance manufacturing sites and /or the drug product manufacturing sites and /or the batch release sites are not considered necessary for the completion of the module 3 assessments however GMP non-compliance for the active substance manufacturing site has been identified. Therefore in context of the Tigecycline Accord application the procedure is not approvable until this issue will be resolved.

GCP

Compliance with GLP and GCP is not applicable as no bioequivalence study is required for this application.

2.5. Type of application and other comments on the submitted dossier

This application concerns a generic centralized procedure and is submitted in accordance with Legal basis 10(1) and Regulation (EC) No 726/2004. Essential similarity is claimed to Tygacil (Tigecycline 50 mg powder for solution for infusion; Marketing Authorization Holder: Pfizer Limited, United Kingdom) approved via centralized procedure on 24 April 2006 (EMEA/H/C/00644).

Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The proposed product is powder for solution for infusion containing Tigecycline as active substance. Tigecycline is a chemical substance and the dosage form has been developed as generic product to the centrally authorised Tygacil ® (Tigecycline 50 mg powder for solution for infusion containing the same active substance in the same pharmaceutical form.

Tigecycline Accord is indicated in adults and in children from the age of eight years for the treatment of the following infections:

• Complicated skin and soft tissue infections (cSSTI), excluding diabetic foot infections

• Complicated intra-abdominal infections (cIAI)

Tigecycline Accord should be used only in situations where other alternative antibiotics are not suitable, ATC Code: J01AA12

3.1.2. Active Substance

General Information

The drug substance Tigecycline is not described in Ph. Eur.

One manufacturer is proposed. ASMF has been submitted by the ASMF holder.

This manufacturer is GMP non-compliant and this is raised as major objection.

A separate active substance dossier for ASMF (including both parts: Applicants part and Restricted part) has been provided. The manufacturing chain of active substance has been satisfactory presented, satisfactory synthesis flow chart and narrative description have been provided. The section Characterisation is satisfactorily addressed.

Acceptable results of the identification tests confirmed the required structure.

The impurities have been discussed and identified, however, the difference between the in-house and USP list of impurities should be discussed and more detail related to one of the impurities is expected. Residual catalysts and solvents are satisfactorily discussed and appropriate control is included in the specification.

Generally acceptable specification has been proposed. For all test acceptable test methods have been proposed. The methods are well described and validated.

The proposed limits are supported by batch results. Generally acceptable description of the packaging material has been provided.

Satisfactory stability study results haves been provided, the conclusion is missing. The proposed re-test period can be accepted if acceptable explanation of storage conditions is provided.

The presented ASMF is generally acceptable, no Major objections are raised.

Specification

The drug substance specification followed by the finished product manufacturer is in line with the drug substance manufacturer's specification

The tests methods are the same as used by drug substance manufacturer.

The batch analysis data for Tigecycline drug substance are all within the specified limits.

The methodologies adopted for various tests against the specification of Tigecycline have been taken from Ph. Eur. monograph, USP monograph, where applicable general chapter and In-house methods.

As the finished product manufacturer proposes the same specification as active substance manufacturer, no additional justification is required.

Comparability exercise for Active Substance

Not applicable.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Tigecycline powder for solution for infusion, 50 mg/vial is an orange lyophilized powder or cake in clear glass vial with flip-off seal. This medicinal product is supplied in vials as a sterile lyophilized powder or cake containing 50 mg/vial of Tigecycline.

The drug product applied for this application is a generic equivalent to Tygacil® (Tigecycline 50 mg powder for solution for infusion; Marketing Authorization Holder: Pfizer Limited, United Kingdom).

The proposed product has the same qualitative and quantitative composition in terms of active substance and same pharmaceutical form as the innovator product Tygacil®.

All excipients were described either with reference to pharmacopoeia (Ph. Eur. or USP) was provided.

The product is supplied in a clear glass vial stoppered with rubber stopper and sealed with aluminium flip-off seal. Information on packaging material and analytical certificates were provided, with minor concerns remaining.

Manufacture of the product and process controls

Names, addresses and responsibility of each manufacturer are provided. The batch formulas for the granulation batch sizes are in line with the proposed composition.

The development and manufacture of the product has been described, with minor concerns remaining. The process is standard for this type of dosage form and minor concerns regarding the manufacture are remaining.

Validation protocols and reports were submitted for three batches. The process validation protocols and reports are used for demonstration that the process for manufacturing Tigecycline 50 mg/vial is being consistently executed within the limits prescribed. Product testing satisfactorily confirms that the critical steps are adequately controlled and consistent such that the finished product meets release specifications.

Product specification

The product specifications cover appropriate parameters for this dosage form - most of the tests meet the requirements of ICH guidelines and Ph. Eur. requirements for parenteral preparations. The pharmacopoeial methods are considered satisfactory. For following specification parameters in-house methods are proposed: description, reconstitution time and identification by UV. Satisfactory descriptions have been provided. The batch analysis results show that the finished products meet the proposed specification. Analytical certificates for three batches have been submitted.

Further concerns regarding control of the drug product remain.

Stability of the product

Shelf life of 24 months is proposed for the finished product and medicinal product does not require any special storage condition.

No potential serious risk to public health is identified. However, there are some points which need to be resolved before the marketing authorization is granted.

Comparability exercise for Finished Medicinal Drug Product

Adventitious agents

3.1.4. Conclusions on the chemical, pharmaceutical and biological aspects

Drug substance

The drug substance Tigecycline is not listed in Ph.Eur. The manufacturer holds ASMF. The manufacturer is GMP non-compliant and major objection is raised.

Specification and tests methods fully comply Ph. Eur. monograph, USP monograph, where applicable general chapter and In-house methods. Description of methods along with their validation has been provided. The quality of drug substance is declared on the presented batch analysis.

Drug product

Tigecycline powder for solution for infusion, 50 mg/vial is an orange lyophilized powder or cake in clear glass vial with flip-off seal. The applicant claims essential similarity, under article 10.1, to Tygacil, powder for solution for injection, which contains the same amount of active substance in the same pharmaceutical form. This reference product MA No EU/1/06/336/01 is held by Pfizer Limited, UK, granted 24.4.2006 in the European Union. The essential similarity of the applicant's formulation with reference formulation has been demonstrated by comparison of composition, impurity profile and other parameters.

The development and manufacture of the product has been described, however there are unresolved concerns remaining.

All the excipients are conventional pharmaceutical ingredients complying with the requirements of European Pharmacopoeia and USNF. The choice of excipients is justified and their functions explained.

There is a single drug product manufacturer and other manufacturing sites for secondary packaging, quality control and batch release.

The product specifications cover appropriate parameters for this dosage form. However, there are some points to be clarified.

Analytical methods are sufficiently described and validated. CoAs of the drug product have been enclosed. The batch analysis results show that the finished product meets the proposed specification.

At this moment the proposed storage conditions and shelf-life cannot be accepted. There are some points which need to be resolved before the marketing authorization is granted.

3.2. Non clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The active substance of Tigecycline Accord 50 mg/vial, powder for solution for infusion is not considered a new active substance. Pharmacodynamic, pharmacokinetic and toxicological properties of tigecycline are well known. As tigecycline is a widely used, well-known active substance, no further studies are required. An overview based on literature review is, thus appropriate. Nevertheless, some shortcomings have been noted in the Non-clinical Overview.

The non-clinical overview report refers to 23 publications.

The non-clinical overview is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required.

However one outstanding issue needs to be clarified by the Applicant.

3.2.1. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant. Since Tigecycline Accord is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

3.2.2. Conclusion on non-clinical aspects

Tigecycline Accord could be approvable from the non-clinical point of view once the outstanding issue will be addressed by the applicant.

3.3. Clinical aspects

The applicant has provided a clinical overview where pharmacology, efficacy and safety of tigecycline were discussed. The active substance of Tigecycline Accord 50 mg/vial, powder for solution for infusion (tigecycline) is not considered a new active substance. Pharmacodynamic, pharmacokinetic, efficacy and safety profiles of tigecycline are well known. As tigecycline is a widely used, well-known active substance, no further studies are required. An overview based on literature review is, thus, appropriate. Information stated in the clinical overview is up-to-date and adequately supported with the scientific literature.

The information in the proposed SmPC has been generally harmonised with the currently approved SmPC of the reference product Tygacil. However, some amendments are needed throughout the SmPC and Package leaflet to be fully in line with the reference product. Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).

3.3.1. Exemption

As this is an abridged license application claiming essential similarity to a currently marketed product, no clinical studies have been undertaken to support the application.

According to the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**),* "bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

The applicant's product Tigecycline Accord powder for solution for injection has the same active substance in the same concentration (after reconstitution) as the reference medicinal product. Furthermore Tigecycline Accord has the same indications, pharmaceutical form, route of administration (intravenous infusion), and the same strength as Tygacil.

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the waiving of bioequivalence studies is therefore deemed acceptable.

3.3.2. Pharmacokinetics

No bioequivalence study was submitted to support the 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 currently approved product.

3.3.3. Pharmacokinetic Conclusion

Tigecycline Accord is considered to be essentially similar to Tygacil.

3.3.4. Pharmacodynamics

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

3.3.5. Additional data

N/A

3.3.6. Post marketing experience

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

3.3.7. Discussion on clinical aspects

The application contains an adequate review of published clinical data. No bioequivalence study is required for this application which is in line with the Appendix II to the Guideline on the Investigation of Bioequivalence.

Tigecycline Accord is considered to be essentially similar to the reference product Tygacil of Pfizer Limited.

3.3.8. Conclusions on clinical aspects

Tigecycline Accord is considered to be essentially similar to the reference product Tygacil of Pfizer Limited. Approval could be recommended from the clinical point of view, provided that the Applicant satisfactory addresses outstanding issues.

4. Pharmacovigilance

4.1. Risk management plan

The applicant has provided Risk Management Plan (RMP) Version 1.0, data lock point 22-Jan-2016, final sign-off 12-Apr-2016. There are nor issues nor concerns for consideration by the PRAC. The document is in line with Risk Management Plan (RMP) for Tygacil Version 12.0, data lock point 30-Sep-2014, final sign-off 03-Dec-2016.

RMP Part II, Module SVIII contains the following summary of safety concerns:

Important identified risks	• Thrombocytopenia • Hepatotoxicity • Anaphylaxis/ anaphylactoid reactions • Pancreatitis • Superinfection
Important potential risks	• QTc prolongation/Torsades de pointes • Pseudomembranous colitis • Lack of efficacy
Missing information	• Use in paediatric patients <8 years of age • Use in pregnant and breast-feeding women • Use in patients on immunosuppressant therapy • Use in patients with neutropenia

The RMP version 12.1 dated 30th March 2015 is the most up to date version for the originator Tygacil. This RMP was updated during procedure EMEA/H/C/000644/II/0092 which received CHMP opinion on 23rd April 2015 with EC Adoption on 28th May 2015. The applicant is requested to update the RMP to be in line with the originators latest RMP. The summary of safety concerns included in the mentioned RMP is the following:

Important identified risks	Thrombocytopenia Hepatotoxicity Anaphylaxis Pancreatitis Superinfection
Important potential risks	QTc prolongation/torsades de pointes *Clostridium difficile*-associated diarrhea and pseudomembranous colitis Lack of efficacy
Missing information	Use in paediatric patients <8 years of age Use in Pregnant women Use in patients on immunosuppressant therapy Use in patients with neutropenia

Only routine pharmacovigilance activities are planned.

No additional risk minimization measures are proposed.

The RMP is needs update, see list of questions.

4.2. Pharmacovigilance system

The applicant has provided Accord Healthcare Limited Pharmacovigilance System Master File Summary. A statement dated 12th April 2016 and signed by the applicant and the qualified person

for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considers that the Pharmacovigilance System Master File Summary fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

5. Overall conclusion and benefit/risk assessment

Although the application contains adequate quality, non-clinical and clinical data and the essential similarity to the reference product has been proved the GMP non-compliance issue regarding API manufacturer preclude the approval of Tigecycline Accord. Moreover minor concerns regarding quality, non-clinical and clinical point of view are remaining.