19 May 2022
EMA/569175/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ertapenem SUN

International non-proprietary name: ertapenem

Procedure No. EMEA/H/C/005815/0000

Note

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

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List of abbreviations

ASMF	Active Substance Master File
CQA	Critical Quality Attribute
EC	European Commission
EEA	European Economic Area
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International conference on harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
KF	Karl Fischer titration
LC/MS	Liquid chromatography/mass spectrometry
LDPE	Low Density Polyethylene
MAH	Marketing Authorisation holder
MS	Mass spectroscopy
NMR	Nuclear magnetic resonance
NMT	Not more than
PDA	Photo diode array
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
RH	Relative Humidity
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant SUN Pharmaceutical Industries (Europe) B.V. submitted on 5 February 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Ertapenem SUN, 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 10 December 2020.

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 the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication

Treatment
Ertapenem SUN is indicated in paediatric patients (3 months to 17 years of age) and in adults for the treatment of the following infections when caused by bacteria known or very likely to be susceptible to ertapenem and when parenteral therapy is required (see sections 4.4 and 5.1):

- *Intra-abdominal infections*
- *Community acquired pneumonia*
- *Acute gynaecological infections*
- *Diabetic foot infections of the skin and soft tissue (see section 4.4 of the SmPC)*

Prevention
Ertapenem SUN is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery (see section 4.4 of the SmPC).

1.2. Legal basis, dossier content

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 and a bioequivalence study with the reference medicinal product Invanz instead of non-clinical and clinical unless justified otherwise.

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: INVANZ, 1g, Powder for concentrate for solution for infusion.
- Marketing authorisation holder: Merck Sharp & Dohme Limited
- Date of authorisation: 18-04-2002

- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/02/216/001-002

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

- Product name, strength, pharmaceutical form: INVANZ, 1g, Powder for concentrate for solution for infusion.
- Marketing authorisation holder: Merck Sharp & Dohme Limited
- Date of authorisation: 18-04-2002
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/02/216/001-002

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP was:

Rapporteur: Hrefna Gudmundsdottir

The application was received by the EMA on	5 February 2021
The procedure started on	25 February 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 May 2021
The PRAC Rapporteur's first Assessment Report was circulated to all	25 May 2021

PRAC and CHMP members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 June 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 January 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	28 February 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 March 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	24 March 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	19 April 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	04 May 2022
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
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 Ertapenem SUN on	19 May 2022

2. Scientific discussion

2.1. Introduction

This application for marketing authorisation is made under article 10(1) generic application of Directive 2001/83/EC as amended. The application refers to the original medicinal product Invanz 1 g powder for concentrate for solution for infusion, marketed by Meck Sharp & Dohme Limited granted via centralised procedure on 18 of April 2002 to Merck Sharp & Dohme Limited.

Ertapenem inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). Like other beta-lactam agents, the mechanism of action of ertapenem involves decreased synthesis of peptidoglycan by inhibition of specific PBP. In *Escherichia coli*, affinity is strongest to PBPs 2 and 3.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 1.0 g ertapenem as active substance.

Other ingredients are sodium hydrogen carbonate (E500), and sodium hydroxide (E524) to adjust pH to 7.5.

The product is available in Type I clear glass vials with a 20 mm grey chlorobutyl rubber stopper and a tear off seal with polypropylene disk as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance is [4R-[3(3S*,5S*),4α,5β,6β(R*)]]-3-[[5-[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid monosodium salt corresponding to the molecular formula $C_{22}H_{24}N_3O_7SNa$. It has a relative molecular mass of 497.5 and the following structure:

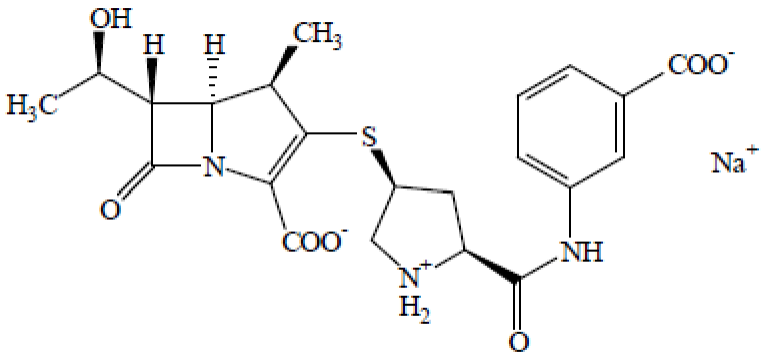

Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of infrared (IR) and ultraviolet (UV) absorption, ^{1}H NMR, ^{13}C NMR, mass spectrum (MS). The solid-state properties of the active substance were measured by XRD.

The active substance is a hygroscopic white to pale yellow powder, freely soluble in water and practically insoluble in ethanol.

The active substance is an optically active molecule having 6 chiral centres. Adequate controls are available in specifications of the intermediate and the starting material to justify control of stereo-chemistry of these moieties.

Polymorphism is not relevant as the medicinal product is used for injectables. Representative X-ray diffraction pattern for three batches of the active is provided. The data presented indicates consistency in polymorphic form.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site. Detailed information on the manufacturing of the active substance has been provided and was considered satisfactory.

During evaluation, the CHMP requested a major objection (MO) on redefinition of one of the initially proposed starting materials, redefinition was performance by the applicant and it was considered satisfactory. The process is described overall in four synthetic steps and a final purification step. The starting materials are well with acceptable specifications.

Critical steps of the synthesis have been clearly stated. 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. During evaluation, the CHMP raised a MO requesting grouped limit for all intermediates containing one of the identified genotoxic impurities to introduce to the specification of the active substance. The applicant agreed to update the active substance specification in this respect and this was considered acceptable,

The active substance is packaged in a triple polybag ((LDPE (inner bag), polyester/LDPE (middle bag), and polyester/aluminium/polyester/LPDE (outer bag))and which is placed in a HDPE drum/container which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description (visual), solubility (visual), identification (IR, HPLC, test for sodium), assay (HPLC), water (KF), pH (Ph. Eur.), bacterial endotoxins (gel clot), assay (HPLC), related substances (HPLC), residual solvents (GC), microbial limits (Ph. Eur), palladium content (ICP-MS), rhodium content (ICP-MS), specific optical rotation (polarimeter), and p-Toluidine (LC/MS/MS).

Limits proposed for related substances are in-line with ICH Q3A and are also based on observed batch analysis data. The level of the dimeric impurities are also in compliance with respective data from the reference medicinal product.

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 impurities testing has been presented.

Batch analysis data (5 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 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 18 months under long term conditions (-20 ± 5°C) according to the ICH guidelines were provided.

The following parameters were tested: description, water, pH, assay, related substances, bacterial endotoxins, and microbial limit test. The analytical methods used were the same as for release and were stability indicating. Ertapenem sodium showed no significant change in any of the test parameters. All the results meet in-house requirements for ertapenem sodium indicating that it is a stable product.

Photostability testing following the ICH guideline Q1B was performed on one batch. The data indicated that there was a change in description. However a significant change was observed in the assay and related substance, hence it is recommended to store the sample in well closed container at -20 ± 5°C.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 18 months when stored in well closed container at -20 ± 5°C in the proposed container.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is lyophilised powder for solution for infusion with the following description:
Dry powder – Off white to pale yellow coloured powder/cake.
After reconstitution – Colourless to yellow coloured solution.

The aim was to develop a stable, robust, generic injectable dosage form which is pharmaceutically equivalent to the reference product Invanz 1 g powder for concentrate for solution for infusion.

The applicant has applied QbD principles in the development of the finished product However, no design spaces were claimed.

The quality target product profile (QTPP) was defined on the basis of the active substance properties, the characterisation of the reference product, taking into account the reference product label and the intended patient population.

The physicochemical characteristics of the active substance have been taken into consideration when developing the finished product. The final formulation of the finished product is an amorphous lyophilizate. During reconstitution it is dissolved in water or saline, therefore no concern is raised regarding the polymorphic form. To evaluate the impact the active substance residual solvents on the related substance of finished product, two batches were manufactured with different levels of residual solvents and charged on stability. The stability data show*ed* that residual solvent of the active substance, resulted in similar impurity profile of finished product at initial and stability. Since the excipients are qualitatively and quantitatively the same no compatibility study between the active substance and the excipients was required.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. The qualitative and quantitative composition of excipients is same as that of the reference

reference product. 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.

The strategy to achieve essential similarity to the reference medicinal product and to obtain a product with similar *in-vivo* performance to the innovator product, was to develop a stable formulation of ertapenem 1 g powder for concentrate for solution for infusion.

The proposed finished generic medicinal product is administered as an aqueous solution for intravenous use containing the same active substance in the same concentration as the currently authorised reference product.

There is no difference between the proposed commercial formulation for marketing and the development formulation. The essential similarity of the generic medicinal product formulation with the reference medicinal product formulation was demonstrated by comparison of the composition and impurity profiles.

In the reference medicinal product information it is stated that Ertapenem for Injection must be reconstituted and then diluted prior to administration of the IV infusion. The reconstituted solution, immediately diluted in 0.9% sodium chloride Injection may be stored at room temperature and used within 6 hours or stored for 24 hours under refrigeration (2-8°C) and used within 4 hours after removal from refrigeration. Solutions of Ertapenem for Injection should not be frozen.

Based on above information, diluents compatibility study was conducted with 10 mL water for injection and 0.9% sodium chloride followed by dilution with 50 ml of 0.9 % Sodium Chloride injection (Final solution conc. – 16.67 mg/mL) respectively, on generic medicinal product development batches and demonstrated that the diluents compatibility was satisfactory.

The primary packaging is Type I clear glass vials with a 20 mm grey chlorobutyl rubber stopper and a tear off seal with polypropylene disk. 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.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site. The manufacturing process consists of 3 main steps: compounding, aseptic filtration and filling followed by lyophilisation The process is considered to be a non-standard manufacturing process as it is an aseptic manufacturing process.

The critical steps of the process and the in-process controls were presented, justified and they are considered acceptable.

The aseptic manufacturing process was validated on three commercial scale finished product batches. Major steps of the manufacturing process have been validated by a number of studies. 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.

Product specification

The finished product release and shelf life specifications shown include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, HPLC-PDA), water (KF), uniformity of dosage units (Ph. Eur.),

residual solvents (GC), sodium content (atomic absorption spectrophotometer), pH (Ph. Eur.), completeness and clarity of solution (visual), particulate matter (visual), reconstitution time (in min), colour absorbance (UV-visible spectrophotometer), particulate matter (Ph. Eur.), related substance (HPLC), assay (HPLC), bacteria endotoxins (Ph. Eur.), sterility (Ph. Eur.), colour solution (Ph. Eur.) and clarity of solution (Ph. Eur.)

The justification, and the acceptance limits of the description, identification, water, uniformity of dosage units, residual solvents, sodium content, pH, constituted solution characteristics (completeness and clarity of solution, particulate matter and reconstitution time, colour absorbance and particulate matter), assay, bacterial endotoxins, sterility, clarity of solution and colour of solution tests are considered acceptable. The calculation of the bacterial endotoxins limit is correct, and it is considered acceptable.

The limits for the unspecified impurities are in-line with ICH Q3B, taking into account the maximum daily dose of Ertapenem and acceptable. The acceptance limits of the specified impurities were established on the basis of batch analysis data, stability data and comparative impurity data between the test and the reference product, batch analysis and stability results. The levels found in the EU reference product can be used to establish limits "qualified by use". The proposed limits for the specified impurities are acceptable.

Based on ICH Q3D Guideline for Elemental Impurities, a risk assessment was performed using Option 2b to determine the probability of inclusion of elemental impurities in the finished product to establish the appropriate controls to ensure the quality of the finished product. The assessment examined the sources of elemental impurities and identified several components that had the potential to transfer elemental impurities into the finished product. In the active substance Palladium (Pd) value is higher than 30 % PDE but controlled in the active substance specification with a specification limit of NMT 7.5 ppm. Thus, it remains at levels below the PDE. Overall the Risk assessment confirms that levels of elemental impurities in Ertapenem for Injection 1g/vial are adequately controlled and no additional controls are required.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested as Major Objection) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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 testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 18 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. In addition to this, stability data has been generated at

intermediate stability condition (30°C ± 2°C / 75% ± 5% RH) for 12 months as significant changes were observed under accelerated stability condition. The batches of the medicinal product are identical representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for tests for description, water, pH, constituted solution (completeness and clarity of solution and particulate matter), reconstituted time, colour absorbance, related substances and assay. The analytical procedures used are stability indicating.

All the parameters are complying to the updated shelf-life specification for the proposed pack till 18 months at long term condition and 12 month at intermediate stability conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. There was no significant change in all tested parameters and data was found within specifications limits after exposure to light. Thus, it can be concluded that finished product is photostable.

In addition to the studies conducted during development, the diluent compatibility and primary reconstitution solution studies were performed on reference medicinal product samples and all three exhibit batches at the finished product with diluents recommended in the reference medicinal product information. Details on preparation and reconstitution prior to administration of the finished product is stated in section 6.6 of the Summary of product characteristics (SmPC).

Based on available stability data, the proposed shelf-life of 24 months without storage conditions as stated in the SmPC (section 6.3 and 6.4) 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. Three issues were raised by CHMP as Major Objections (MO) related to redefinition of starting material, control of genotoxic impurities in the active substance and nitrosamine risk assessment. The issue was resolved satisfactorily by the applicant.

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.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

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. Recommendations for future quality development

Not applicable

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.

2.3.2. Ecotoxicity/environmental risk assessment

No environmental risk assessment was submitted. This was justified by the applicant as the introduction of Ertapenem SUN manufactured by Sun Pharmaceutical Industries Europe B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all ertapenem containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

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. The Overview based on literature review is appropriate.

Pharmacodynamic, pharmacokinetic and toxicological properties of ertapenem are well known. As ertapenem is a widely used, well-known active substance, the applicant has not provided additional studies.

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

2.3.4. Conclusion on the non-clinical aspects

The non-clinical aspects are considered adequate to support this application. There are no objections to the approval of Ertapenem SUN from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a powder for concentrate for solution for infusion containing ertapenem.

The reference product is Invanz, 1 g powder for concentrate for solution for infusion, by Merck Sharp & Dohme B.V., a centralised product (EMEA/H/C/389).

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 (Rev.1) in its current version is of particular relevance.

Exemption

No bioequivalence study was submitted to support the application. According to Appendix II of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98), 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 reference product. This is the case for Ertapenem SUN. Furthermore, the product applied for and the reference product contain the same excipients. A bioequivalence study was thus not required.

Ertapenem SUN, is considered essentially similar to Invanz by Merck Sharp & Dohme B.V.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

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

2.4.2.2. Pharmacodynamics

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

2.4.2.3. Post marketing experience

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

2.4.3. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate.

No bioequivalence study was submitted to support the application, this is in accordance with Appendix II to the Guideline on the Investigation of Bioequivalence.

Ertapenem SUN is considered essentially similar to Invanz.

2.4.4. Conclusions on clinical aspects

The application contains an adequate review of published clinical data.

There are no objections to an approval of Ertapenem SUN from a clinical point of view.

2.5. Risk Management Plan

2.5.1. Safety concerns

The applicant identified the following safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

This is in line with the reference Medicinal Product.

Having considered the data in the safety specification it is agreed that the safety concerns listed by the applicant are appropriate.

2.5.2. Pharmacovigilance plan

2.5.2.1. Routine pharmacovigilance activities

The Applicant has not proposed other routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

2.5.2.2. Summary of additional PhV activities

The Applicant has not proposed additional pharmacovigilance activities.

2.5.2.3. Overall conclusions on the PhV Plan

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.5.3. Risk minimisation measures

2.5.3.1. Routine Risk Minimisation Measures

Not applicable for this generic medicinal product with no new active substance, where the originator product does not have additional risk minimisation activities.

2.5.3.2. Summary of additional risk minimisation measures

Not applicable for this generic medicinal product with no new active substance, where the originator product does not have additional risk minimisation activities.

2.5.3.3. Overall conclusions on risk minimisation measures

The PRAC, having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan (version 0.3, submitted with the Applicant's responses to the LoOI) is acceptable.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.7.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons: Space constraints on the immediate packaging material (vial label).

3. Benefit-risk balance

This application concerns a generic version of ertapenem powder for concentrate for solution for infusion. The reference product Invenz is indicated for:

Treatment

INVANZ is indicated in paediatric patients (3 months to 17 years of age) and in adults for the treatment of the following infections when caused by bacteria known or very likely to be susceptible to ertapenem and when parenteral therapy is required:

- *Intra-abdominal infections*
- *Community acquired pneumonia*
- *Acute gynaecological infections*
- *Diabetic foot infections of the skin and soft tissue*

Prevention

INVANZ is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery.

No non-clinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance. The applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

Ertapenem SUN is considered essentially similar to the reference product.

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

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ertapenem SUN is favourable in the following indication:

Treatment
Ertapenem SUN is indicated in paediatric patients (3 months to 17 years of age) and in adults for the treatment of the following infections when caused by bacteria known or very likely to be susceptible to ertapenem and when parenteral therapy is required (see sections 4.4 and 5.1):

- *Intra-abdominal infections*
- *Community acquired pneumonia*
- *Acute gynaecological infections*
- *Diabetic foot infections of the skin and soft tissue (see section 4.4 of the SmPC)*

Prevention
Ertapenem SUN is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery (see section 4.4 of the SmPC).

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 medical prescription.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.