25 February 2016
EMA/620892/2016
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Ertapenem Hospira

International non-proprietary name: ertapenem sodium

Procedure No. EMEA/H/C/4080/0000

Note

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

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Table of contents

List of abbreviations

AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
IM	Intramuscular
IR	Infrared Spectroscopy
IV	Intravenous
MA	Marketing Authorisation
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance spectroscopy
UV	Ultraviolet Spectroscopy

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the generic application for *Ertapenem Hospira 1 g powder for concentrate for solution for infusion* in the claimed indications

Treatment

Ertapenem Hospira 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)

Prevention

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

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

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section 6).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

1. Synthetic process from proposed starting materials to final drug substance contains only two steps. The starting materials for ertapenem sodium should be redefined to ensure the quality of the drug substance,
2. Consistency / validity of the non-standard manufacturing process of the drug product has not been demonstrated reliably,
3. Method for determination (calculation) of related substances,
4. Based on the stability results provided by the Applicant a shelf life cannot be defined for the drug product.

Deficiencies arising from concerns over the confidential part of the ASMF are mentioned in the appendix (this appendix should not be disclosed to the Applicant). These concerns will be conveyed in confidence to the holder of the ASMF.

Proposal for questions to be posed to additional experts

Proposal for inspection

GMP inspection(s)

No GMP inspection is suggested.

GCP inspection(s)

Not applicable. Clinical studies were not conducted.

2. Executive summary

2.1. Problem statement

Not applicable for generic applications.

2.2. About the product

Ertapenem is a long-acting, parenteral, group 1, 1-β-methyl carbapenem antibiotic with broad spectrum antibacterial activity. It is active against gram-positive and gram-negative bacteria. It binds to penicillin binding proteins (PBP) and inhibits the cell wall synthesis in bacteria. Ertapenem is structurally related to β-lactam antibiotics. The proposed therapeutic indications of the applied generic medicinal product Ertapenem Hospira are, similar to the originator Invanz, as follows:

Treatment

Ertapenem Hospira 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)

Prevention

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

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

In treatment of bacterial infections the dosage in adults and adolescents (13 to 17 years of age) is 1 gram once a day given by intravenous infusion once daily. In infants and children (3 months to 12 years of age) the dosage is 15 mg/kg twice daily, not to exceed 1 gram/day. To prevent surgical site infections following elective colorectal surgery in adults, the recommended dosage is 1 g administered as a single intravenous dose to be completed within 1 hour prior to the surgical incision. Dose

adjustment is not necessary in patients with hepatic impairment or adult patients, including the elderly, with mild to moderate renal impairment (creatinine clearance > 30 ml/min/1.73 m^2).

Ertapenem Hospira is to be administered as an aqueous intravenous solution containing the same active drug substance in the same concentration as the reference product Invanz. The excipients are not considered to affect distribution of the active substance. Bioequivalence studies are not needed, in accordance with the guideline CPMP/EWP/QWP/1401/98 Rev.1.

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

The applicant did not receive CHMP or Member State Scientific Advice.

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

A certificate of GMP compliance has been provided for the drug substance manufacturer by MHRA.

A QP declaration has been provided by the Hospira UK certifying that the active ingredient is manufactured in compliance with GMP for starting materials.

The manufacturing site for final product is approved by MHRA.

GCP aspects are not applicable: Clinical studies were not conducted.

Two toxicological studies conducted (a 28-day intravenous (IV) subchronic toxicity study in rats and a single-dose intramuscular (IM) local tolerance study in rabbits of Ertapenem Hospira for Injection and Invanz) were GLP-compliant studies.

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

- Legal basis

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Ertapenem Hospira 1 g powder for concentrate for solution for infusion. The Applicant is Hospira UK Limited.

The originator product is Invanz 1 g powder for concentrate for solution for infusion (EMEA/H/C/000389), marketing authorisation holder Merck Sharp & Dohme Ltd. and registered within the community since 18-Apr-2002.

3. Scientific overview and discussion

3.1. Introduction

3.2. Quality aspects

3.2.1. Introduction

Ertapenem Hospira 1 g powder for concentrate for solution for infusion is available as a sterile lyophilized powder/cake, which is intended for dilution with a suitable intravenous solution prior to administration. The drug product is a white to pale yellow powder/cake presented in a 20 ml, clear

tubular Type – I glass vial. Active substance is ertapenem sodium. One vial contains 1.046 g ertapenem sodium equivalent to 1 g ertapenem.

Quality overall summary is provided. Information on the quality expert (dated 20th October 2015) is presented.

3.2.2. Active Substance

General Information

Ertapenem is a carbapenem antibiotic which is structurally related to β-lactam antibiotics. It contains the 4:5 fused carbapenem ring system, which is common to all carbapenem antibiotics. Ertapenem is used as a sodium salt in Ertapenem Hospira drug product. Chemical name of the molecule is [4*R*,5*S*,6*S*]-3-[[(3*S*,5*S*)-5-[[(3-Carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monosodium salt. Ertapenem sodium is white to pale yellow hygroscopic granular powder. It is freely soluble in water and dimethyl sulfoxide, slightly soluble in methanol and practically insoluble in acetonitrile.

Molecule contains six chiral centers and the chirality is controlled with specific optical rotation in the specification since pure isomer is used. Ertapenem has three ionisable moieties which are relevant to its physicochemical properties but only one pKa has been reported. Partition coefficient has been reported as -4.2 without any details. However, the reported value probably refers to apparent partition coefficient (distribution coefficient) rather than the partition coefficient of the unionized species.

Ertapenem sodium drug substance is mostly amorphous but it also contains crystalline material. The amount of crystalline material in the drug substance has not been determined and also the polymorphic form is not known. The drug substance is hygroscopic and readily absorbs moisture. Ertapenem sodium does not have a clear melting point but starts to decompose at 220°C.

Manufacture, characterisation and process controls

Ertapenem sodium is manufactured by only one manufacturing site. Information on the drug substance has been provided in the form of active substance master file (ASMF).

Synthesis of the drug substance consists of two steps.

The structure of ertapenem sodium is confirmed by ultraviolet spectroscopy (UV), infrared spectroscopy (IR), mass spectrometry (MS) and nuclear magnetic resonance spectroscopy (NMR). Elemental analysis results for carbon and hydrogen were not very close to theoretical values. Content of sodium was determined and it was close to theoretical value in all the tested batches. The provided spectroscopic data is consistent with the proposed 2D molecular structure, but cannot confirm the stereochemistry of the drug substance.

The proposed synthetic process consists of two steps. All the reactions affecting the stereochemistry of the drug substance are done prior to the introduction of starting materials. Therefore the reactions are not done under GMP. The stereochemistry of the drug substance is controlled by specific optical rotation. However, specific optical rotation is not a specific method since the obtained result is a net result of all the optically active compounds in the sample. The values obtained with specific optical rotation do not have any reference since there are no official reference standards available. The short two-step synthetic process can be problematic if changes are made to the synthetic process of starting materials. New impurities might be introduced to drug substance since there is less chance that these

impurities would be cleared during the short two-step process. The starting materials should be redefined to ensure the quality of the drug substance.

Specification

Ertapenem sodium does not have a monograph in Ph. Eur. or USP. The specifications and acceptance criteria are based on ICH recommendations, general compendial requirements, batch analysis data and assessment of the reference drug product.

Specifications used by the drug substance manufacturer and drug product manufacturer are slightly different. Drug product manufacturer has tighter limits for related substances. The impurity limits used by the drug substance manufacturer should be lowered to better resemble the batch analysis and stability data. Additionally, it should be clarified how the amount of impurities in drug substance are calculated. It appears that similar UV response is assumed for ertapenem and all the related substances. This should be proved by presenting relative response factors (RRF) for impurities. The limits for heavy metals, content of palladium and residual solvents based on ICH recommendations and therefore are considered acceptable. There is no upper limit for sodium in the specification.

The amount of water in drug substance affects the degradation by enabling hydrolysis and therefore the amount should be minimized. The limit for water is considered too high, according to the water content in batch analysis and in stability studies.

Limits for specific optical rotation have been set between -10° and -18°. The stereochemistry of the final drug substance has been proved by synthesis. However, specific optical rotation limits set for intermediates and starting materials also do not have a reference and absolute configurations of these molecules have not been proved. More detailed information should be provided to ensure that the proposed specific rotation actually corresponds to the desired absolute configuration.

Stability

Stability studies have been presented for three batches manufactured in 2013 (EDXU130004, EDXU130005, EDXU130006) and three batches manufactured in 2014 (EDXE140001, EDXE140002, EDXE140003). EDXU batches are intended for US market and EDXE are intended for EU market.

24 months of long term stability data at -20°C is available for batches manufactured in 2013 and six months long term stability data is available for batches manufactured in 2014. Significant changes have been observed for highest unknown impurity after 18 months for batches EDXU130004, EDXU130005 and EDXU130006. Accelerated studies with four batches (EDXE140001, EDXE140002, EDXE140003, EDXE140004) have been performed for 60 days at 2-8°C and for 48 hours at 25°C ± 2°C / 60% RH ± 5%RH. The stability studies have been performed according to ICH guidance for a drug substance which is intended to be stored in a freezer. The parameters tested in the stability study are stability indicating.

The amount of all related substances increases in stability studies except a process related impurity. Stability of the drug substance would be different if more water was present in the drug substance. Lack of mass balance can be seen in the stability data. The amount of impurities formed is much less than the decrease of assay value. This lack of mass balance should be explained. Possible reasons could be that relative response factors have not been determined for the impurities and therefore some of the impurities may be underestimated. There is also a possibility that some other impurities are formed which are not taken into account or which are not detected by the related substances HPLC method used.

Long term stability data should be available for EDXE batches for 12 months by now and the updated stability data should be provided. Updated stability data will enable to better evaluate the limits set for impurities and assay in the specification. The proposed retest period of 6 months, when the drug substance is stored at -20°C, is considered acceptable.

Comparability exercise for Active Substance

N/A

3.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Ertapenem 1 g powder for concentrate for solution for injection is available as a sterile lyophilized powder/cake, which is intended for dilution with a suitable intravenous solution prior to administration. The drug product is a white to pale yellow powder/cake presented in a 20 ml, clear tubular Type – I glass vial. The vials are stoppered with grey bromobutyl lyophilisation rubber stoppers and white coloured flip-off seal. This is an aseptically filled sterilized product containing no antimicrobial preservatives. The pH range of the reconstituted solution is from 7.0 to 8.5. A clear colourless to yellow colour solution results when the powder is reconstituted with diluent as directed in the labelling. The reconstituted solution should be diluted in sodium chloride 9 mg/ml (0.9%) solution immediately after preparation.

The active ingredient, route of administration, dosage form and strength of Ertapenem 1 g powder for concentration for solution for infusion is the same as that of the innovator product Invanz 1 g powder for concentrate for solution for infusion manufactured by Merck. The excipients used in the formulation are the same excipients as those in the innovator product. Hospira´s product contains 175 mg of sodium hydrogen carbonate, the same amount listed in the package insert for the innovator.

Ertapenem drug substance is heat sensitive and susceptible to degradation outside a very narrow pH range. Based on the thermolabile nature of the drug substance the aseptic filtration and filling into pre-sterilised vials followed by lyophilisation is justified. Further it is reported that the dimers are formed when the ertapenem concentration is high, i.e. >100 mg/ml and the Ertapenem product with higher water content (about 5%) showed significant increase in hydrolysed impurity during the stability studies.

Development work evaluating formulation and manufacturing process is presented and is generally satisfactory. Physicochemical characterization of the innovator product was performed during development work. Comparative batch data of Hospira´s Ertapenem and innovator product Invanz show a different level of related substances. It is also remarked that the batch results for Hospira´s products are release data and the innovator product has been tested closer to the expiry date.

Different attributes of the drug product like headspace of the vial, effect of the sodium bicarbonate content of drug product, effect of the bulk solution pH (adjusted using sodium hydroxide), effect of the bulk solution concentration and the impact of water content of the lyophilized product was evaluated during development of the drug product formulation.

The proposed formulation consists of 6% excess to compensate for degradation during manufacture and 4% excess to compensate for degradation during the in-use storage period of the reconstituted solution. In addition overfill of 4% is to compensate for the non-withdrawable amount. The overages are considered justified. Manufacturing process parameters were determined through feasibility

studies. Critical attributes investigated included: bulk solution pH, temperature, bulk solution hold time, filter compatibility / validation and lyophilisation cycle parameters. Based on the development studies the target cycle of the lyophilisation has been defined; however during manufacture / process validation the target cycle has been modified.

The container closure system for Hospira´s Ertapenem 1 g powder for concentrate for solution for infusion is consistent with that of the innovator product Invanz. Container closure integrity studies have been performed. The suitability of the proposed closure formulation was confirmed during stability studies.

Manufacture of the product and process controls

Manufacturing process of Ertapenem 1 g / vial involves the following steps: 1. preparation / compounding of bulk solution, 2. Filtration of bulk solution, 3. Filling and partial stoppering of the vials, 3. Lyophilisation, 4. Sealing, 5. Labelling and packaging.

Ertapenem 1g powder for concentrate for solution for infusion is manufactured by aseptic filtration and filling into pre-sterilized vials followed by lyophilisation.

The in-process controls include description, pH, bioburden and assay of the bulk solution. During filling step weight / filling volume are controlled. The lower in-process limit proposed for assay of bulk solution is not acceptable. Limits for fill weight are not given. Further, there are several discrepancies in different sections of the dossier concerning description of manufacturing process, which should be clarified.

The major concern is validity / consistency of the manufacturing process. Based on the process validation data presented in the application it cannot be concluded that the product uniformity is maintained throughout the manufacturing process. The three proposed validation batches are of pilot scale. Further the validation data presented in the dossier do not provide sufficient evidence that the process can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes. In addition several modifications have been done to the manufacturing process (e.g. lyophilisation). Further, it is considered that the two recent validation / stability batches do not fulfil the shelf life specification up to the end of the proposed shelf life. Hence, considering the degradation sensitivity of the product, non-standard manufacturing method, the dosage form and administration also for small children reliable proof on the product uniformity throughout the manufacturing process with full scale production batches as required by NfG on process validation (CPMP/QWP/ 2054/03 // EMA/CHMP/CVMP/QWP/BWP/70278/2012/Rev1) should be presented.

Product specification

The parameters included in the specification of Ertapenem 1g powder for concentrate for solution for infusion are mainly acceptable for the type of dosage form and in line with the Ph. Eur. and ICH Q6A requirements for parenteral products.

However, a parameter of total dimers should be included in the specification. Further, some acceptance limits are not sufficiently justified. The assay limits proposed for release / shelf life are not justified and should be tightened. Similarly, based on the development studies limits for water content and pH are not justified. With respect to the limits for impurities, Hospira informs that toxicity studies were performed to qualify these impurities up to twice the level in the drug product (i.e. 2 times the level in the Certificate of Analysis). However, according to the toxicological assessment further toxicological

justification is required for the proposed specification limits at the shelf life of the degradation products. It is also remarked that the specification limits of impurities should be based on the release and stability data.

Analytical methods are validated according to the ICH Q2 (R1) for all appropriate parameters. However, the mass balance between assay and degradation products during stability testing should be discussed / shown. In some studies the assay results are fluctuating heavily. This should be clarified. There are also some questions on determination of content of ertapenem and related substances which should be clarified. In addition the proposed use of theoretical fill weight i.e. 1080 mg in the calculation of related substances instead of label claim i.e. 1000 mg is not acceptable.

Stability of the product

Stability of the product is one of the major concerns regarding the Ertapenem 1 g. Stability studies were performed according to the ICH stability guidelines. The parameters tested are stability indicating and the analytical methods have been validated for stability testing. To date results of 6 months accelerated / 24 months long term for one batch and 6 / 9 months for two other batches are provided. However, the Applicant´s summary / discussion on the stability results is very general. No critical evaluation has been made on stability of the product.

Results of photo-stability testing show that the product is not photo sensitive. It can also be agreed that the results of temperature cycling show that thermal stress cycling of 12 days had only little to no impact on the stability of the Ertapenem for injection.

However, the formal stability data provided by the Applicant do not support the proposed shelf life of 2 years. The increase of the degradation products in recent stability batches is expected to exceed the specification limits after 2 years (when the product is reconstituted at the latest). It is also remarked, that the use of the revised calculation method for related substances underestimates the impurities.

Further, the stability / compatibility results of reconstituted product do not support storage of Ertapenem for injection for up to 6 hours at room temperature and 24 hours at refrigerated conditions (2-8°C) followed by 4 hours at room temperature as proposed by the Applicant. Hospira´s product used in the study was just released. The samples closer to the expiry date should be used in the compatibility / stability study. Mass balance between the assay and related substances has not been discussed / shown. It is also considered that the quality / stability of the batch used in the compatibility study differs from the recent EU-batches. Further, it is pointed out that the reconstituted product should comply with the shelf life specification of the finished product during the proposed in-use storage if no separate shelf life specifications are proposed and justified for the reconstituted product. It is also remarked that according to the SPC: “Compatibility of Ertapenem Hospira with intravenous solutions containing heparin sodium and potassium chloride has been demonstrated”. However, no compatibility data are provided on Ertapenem Hospira with solutions containing heparin sodium and potassium chloride.

Comparability exercise for Finished Medicinal Drug Product

N/A

Adventitious agents

It is confirmed that none of the materials used during manufacture of this product are affected by the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents

via Human and Veterinary Medicinal Products (EMEA/410/01 Rev. 3). It is also declared that no starting material of bovine or caprine origin is used in the manufacture of ertapenem sodium and therefore it is in compliance with the EMEA/410/01 Rev.3 .

3.2.4. Discussion on chemical, pharmaceutical and biological aspects

Generally the Module 3 (quality) of the dossier meets the relevant EU guidelines. Also the material provided in active substance master file concerning the drug substance is considered adequate. However, based on the review of the data on quality, it is considered that the generic application for Ertapenem Hospira 1g powder for concentrate for solution for infusion is not approvable since "major objections" have been identified. Major pharmaceutical objections to the application apply to definition of the starting materials for drug substance ertapenem sodium, consistency / validity of the manufacturing process of the finished product, determination of related substances and stability of the drug product. Also several points for clarification are raised.

The proposed two-step synthesis process for the drug substance is considered too short to ensure the quality of drug substance. All the important synthetic steps affecting the structure and stereochemistry of the drug substance are performed prior to the proposed starting materials. Therefore most of the synthesis steps required to produce the drug substance are not done under GMP. The starting materials should be redefined and the dossier and ASMF should be updated accordingly. In addition, there are several other concerns that should be also addressed before the quality of drug substance can be considered acceptable.

Based on the data given in the dossier the stability of the finished product and consistency of the manufacturing process have not been reliably shown. Ertapenem drug substance is heat sensitive and susceptible to degradation outside a very narrow pH range. Further it is reported that the dimers are formed with high Ertapenem concentration (>100 mg/ml) and with higher water content the product showed significant increase in hydrolysed impurity during the stability studies. Hence, considering the degradation sensitivity of the product, non- standard manufacturing method (sterile filtration / lyophilisation), the dosage form (parenteral product) and administration also to infants the validity of the manufacturing process should be demonstrated more reliably with full production scale batches in accordance with the NfG on process validation (CPMP/QWP/2054/03). Stability studies were performed according to the ICH stability guidelines. However, the formal stability data provided by the Applicant do not support the proposed shelf life of 2 years. It is also remarked, that the use of the revised calculation method for related substances underestimates the impurities. Further, the stability / compatibility results of reconstituted product do not support the proposed in-use storage times for Ertapenem for injection.

3.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Ertapenem is a synthetic carbapenem antibiotic which is used as a sodium salt. Ertapenem sodium does not have a monograph in Ph. Eur. or USP. Information on the drug substance has been provided in the form of active substance master file (ASMF). Based on the data presented in the ASMF the ertapenem sodium drug substance is not considered acceptable yet for the intended use in the Ertapenem 1 g concentrate for solution for infusion.

The active ingredient, route of administration, dosage form and strength of Ertapenem 1 g powder for concentration for solution for infusion is the same as that of the innovator product Invanz® 1 g powder for concentrate for solution for infusion manufactured by Merck. The excipients used in the formulation are the same excipients as those in the innovator product. Hospira´s product contains 175 mg of

sodium hydrogen carbonate, the same amount listed in the package insert for the innovator. Hence, the Ertapenem 1 g is very similar with the innovator product Invanz. However, based on the data provided by the Applicant there is a concern on the consistent quality / stability of the product. From quality point of view similarity of Ertapenem Hospira with the innovator product cannot be confirmed.

3.3. Non clinical aspects

3.3.1. Pharmacology

N/A

3.3.2. Pharmacokinetics

N/A

3.3.3. Toxicology

Ertapenem has been in medicinal use in the EU for more than 10 years, with an acceptable level of safety. The Impurity profile of Ertapenem Hospira for Injection (1 g Powder for Concentrate for Solution for Infusion) differed from the originator in the quantities. This application includes two new GLP-compliant toxicological study reports, a 28-day intravenous (IV) subchronic toxicity study in rats and a single-dose intramuscular (IM) local tolerance study in rabbits of Ertapenem Hospira for Injection and Invanz for the toxicological characterization and qualification of the impurities of Ertapenem Hospira for Injection.

Six impurities were identified in Ertapenem Hospira for Injection (also present in Invanz®), of which 4 impurities exceeded International Conference on Harmonisation (ICH) specified impurity limits. Ertapenem Hospira for Injection also contains higher levels of impurities when compared to Invanz® marketed by Merck Sharp & Dohme Limited, Hertfordshire (UK).

The non-clinical overview dated on July 2015 is based on 49 relevant publications since 2000.

A Comparative 28-Day intravenous toxicity study of Ertapenem Hospira for Injection including 14-Day recovery period in Sprague-Dawley rats *(Study 72243)* was conducted to evaluate the potential subchronic toxicity and reversibility of any changes of the Ertapenem Hospira for Injection and to compare the toxicity profile of Ertapenem Hospira for Injection to that of Invanz®. Rats received once daily bolus IV injection of Ertapenem Hospira for Injection or Invanz® (or vehicle control) at 100 mg/kg/day (1 x HED of the active substance based on the maximum daily dose of 1 g of ertapenem and body surface area) and 200 mg/kg/day (2 x HED). The treatment with Ertapenem Hospira for Injection was well tolerated and resulted overall in a similar toxicity profile as the reference product Invanz®. The differences in the responses between the Ertapenem Hospira for Injection and Invanz included minimal increases in the cellularity of the germinal center associated with the increase in the spleen weights. The mechanism of this reversible effect is unknown. The findings were considered non-adverse and unlikely to be of clinical relevance since these were low in frequency and reversible after interruption of ertapenem treatment, and not associated with other notable clinical observations or clinical pathology findings.

A Comparative single-dose intramuscular local tolerance study of Ertapenem Hospira for Injection in New Zealand White rabbits (*Study 72242B*) was conducted to evaluate and compare the local irritation of the Ertapenem Hospira for Injection and Invanz®. The rabbits were administered with a single dose IM injection (0.55 mL) of 162 mg/animal of Ertapenem Hospira for Injection or Invanz®. A higher

incidence of the treatment-related injection site reactions was noted in the Ertapenem Hospira for Injection –treated animals as compared to the Invanz® -treated animals. No mortalities were seen in animals treated with Ertapenem Hospira for Injection, but one death occurred in the Invanz® -treated group for which the reason remained unresolved. Although there were differences observed in the frequency and magnitude in the injection site reactions between the Ertapenem Hospira for Injection and the originator Invanz®, the findings were reversible and previously known to be related to the ertapenem treatment.

In conclusion, there are some differences between the Ertapenem Hospira for Injection and the originator in the toxicological studies in rats and rabbits, but the findings were low in frequency and reversible after interruption of ertapenem treatment, and considered unlikely to be of clinical relevance. However, some acceptance limits proposed for the impurities at shelf-life are not sufficiently justified. Part of the degradation product impurities in the repeated dose toxicity impurity qualification study, even at the highest tested dose (200 mg/kg/day), the doses of these impurities appear to be below the respective human equivalent doses at the drug product shelf-life specification limits.

3.3.4. Ecotoxicity/environmental risk assessment

Ertapenem Hospira for Injection manufactured by Hospira is 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 risk to the environment is expected to be similar and not increased.

3.3.5. Discussion on non-clinical aspects

The toxicological studies conducted for the toxicological characterization and qualification of the impurities of Ertapenem Hospira for Injection are considered adequate.

Some differences in the findings were noted between the Ertapenem Hospira for Injection and the originator in the toxicological studies in rats and rabbits associated with the spleen and in the incidence of the treatment-related injection site reactions. These findings were low in frequency, not associated with other notable clinical observations or clinical pathology findings and were reversible after interruption of ertapenem treatment, and thus considered unlikely to be of clinical relevance.

However, some acceptance limits proposed for the impurities at shelf life are not sufficiently justified. Further toxicological justification is asked for the Applicant's proposal to qualify impurity levels at shelf-life up to 2x of the levels in the Certificate of Analysis, based on the maximum daily dose (1g) of ertapenem and body surface area. Part of the degradation product impurities i.e. Dimer IV and Oxazinone impurity in the repeated dose toxicity impurity qualification study, even at the highest tested dose (200 mg/kg/day), the doses of these impurities appear to be below the respective human equivalent doses at the drug product shelf-life specification limits.

3.3.6. Conclusion on non-clinical aspects

There are no non-clinical major objections to approval of Ertapenem Hospira 1 g Powder for Concentration for Solution for Infusion. However, there are issues that need to be clarified related to the qualification of proposed shelf-life impurity levels, see list of questions.

3.4. Clinical aspects

3.4.1. Exemption

No bioequivalence studies were submitted.

Referring to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), the applicant claims that a bioequivalence study is not required for this application since Ertapenem Hospira is to be administered as an aqueous IV solution containing the same active drug substance (ertapenem; as ertapenem sodium) in the same concentration as the reference product Invanz.

The excipients used in the applied product are sodium bicarbonate and sodium hydroxide; please refer to the Quality assessment for complete composition. These excipients are not considered to affect distribution of the active substance.

Bioequivalence studies are not needed, in accordance with the guideline CPMP/EWP/QWP/1401/98 Rev.1/ Corr **.

3.4.2. Pharmacokinetics

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

3.4.3. Pharmacodynamics

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

3.4.4. Additional data

Not applicable.

3.4.5. Post marketing experience

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

3.4.6. Discussion on clinical aspects

According to 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 different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

Ertapenem Hospira 1 g Powder for Concentration for Solution for Infusion is to be administered as an aqueous IV solution containing the same active drug substance in the same concentration as the reference product Invanz. The existing differences in the excipients of the applied product as compared to the reference product are not expected to have any significant impact in properties with regards to bioavailability, pharmacokinetics, safety and efficacy between these products.

The requirements set out in the bioequivalence guideline are considered met, and a waiver of bioequivalence study is considered acceptable from a clinical point of view, provided the product is deemed to be essentially similar to the reference product based on the pharmaceutical and non-clinical assessment.

The clinical overview supports the indications and covers adequately the biopharmaceutics, clinical pharmacology, efficacy and safety of the product.

The proposed therapeutic indications, posology and method of administration of Ertapenem Hospira are identical with the SmPC of Invanz. A few updates to the proposed product information are required in line with the product information of the reference product. Please refer to the annexed product information for detailed comments.

3.4.7. Conclusions on clinical aspects

There are no major objections to approval of Ertapenem Hospira 1 g Powder for Concentration for Solution for Infusion from a clinical point of view, provided the product is deemed to be essentially similar to the reference product based on the pharmaceutical and nonclinical assessment. The product information should be updated in line with that of the reference product Invanz.

3.5. Risk management plan

Summary of safety concerns

The Applicant identifies the following safety concerns:

Summary of safety concerns	
Important identified risks	• Serious anaphylactic reactions • Superinfection • Antibiotic-associated colitis and pseudomembranous colitis • Seizures • Use in breast feeding mother • Diarrhoea • Infused vein complication • Infusion site pain • Nausea • Elevation in aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase and platelet count • Decrease in neutrophil count
Important potential risks	• Use in pregnancy • Effect on fertility in men and women • Use in the treatment of severe infection • Risk of potential treatment failure due to suboptimal exposure to ertapenem during surgical intervention exceeding four hours
Missing information	• Use in paediatric population (children under 3 months of age) • Use in severe renal impairment • Use in patients on haemodialysis • Effects on the ability to drive and use machines
Important identified interactions	• Concomitant use with valproic acid

The following issues should be addressed:

In line with the reference product, the following safety specification should be followed:

Important identified / potential risks:

- Hypersensitivity/anaphylactic reactions
- Drug interactions with valproic acid or divalproex sodium
- Drug interaction with probenecid
- Pseudomembranous colitis
- Drug resistance
- Seizure

Important missing information

- Use in pregnancy
- Use in patients < 3 months of age

3.6. Pharmacovigilance system

The pharmacovigilance system as described by the applicant 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.

4. Orphan medicinal products

N/A

5. Overall conclusion and benefit / risk assessment

The application contains adequate non-clinical and clinical data. However, the quality data are inadequate and from quality point of view similarity of Ertapenem Hospira with the innovator product cannot be confirmed at present. The aspects that are inadequately demonstrated are outlined in the List of Questions.

The Rapporteur, 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.

5.1. Conclusions

The overall B/R of Ertapenem Hospira 1 g powder for concentrate for solution for infusion is negative at the present time.