EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Evaluation of Medicines for Human Use

Assessment Report

Topotecan Hospira

International Non-proprietary Name: topotecan

Procedure No. EMEA/H/C/001192

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Hospira UK Limited submitted on 3 June 2009 an application for Marketing Authorisation to the European Medicines Agency for Topotecan Hospira, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(3) of Directive 2001/83/EC.
The chosen reference product is:

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

- Product name, strength, pharmaceutical form: **Hycamtin® 4mg Powder for Concentrate for Solution for Infusion**
- Marketing authorisation holder: **SmithKline Beecham Plc**
- Date of authorisation: **12-11-1996**
- Marketing authorisation granted by:
  - Community
- (Community) Marketing authorisation number:):
  5 vials: EU/1/96/027/001
  1 vial: EU/1/96/027/003

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- **Not applicable**

The Rapporteur appointed by the CHMP was: Dr. Gonzalo Calvo

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 3 June 2009.
- The procedure started on 24 June 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 September 2009 (Annex 4.1).
- During the meeting on 19-22 October 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 October 2009 (Annex 4.2).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 November 2009.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 January 2010 (Annex 4.3).
- During the CHMP meeting on 18-20 January 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant (Annex 4.4).
- The applicant submitted the responses to the CHMP list of outstanding issues on 15 February 2010.
- During the meeting on 15-18 March 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Topotecan Hospira on 18 March 2010.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Topotecan Hospira 4mg/4ml concentrate for solution for infusion is a hybrid medicinal product containing topotecan hydrochloride as active substance. It is intended for intravenous infusion only after dilution with either sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection, resulting in a final concentration between 25 and 50 micrograms/ml in the solution for infusion. The reference medicinal product Hycamtin 4 mg powder for concentrate for solution for infusion has been centrally authorised on 12 November 1996. The reference product has also been registered at a dose of 1 mg; Hospira didn't apply for a 1mg/1ml presentation of this product. The active substance of the reference product is topotecan also present as topotecan hydrochloride salt. The difference compared to this reference medicinal product is a change in the pharmaceutical form, which results in the non inclusion of Mannitol.

Topotecan is a cytotoxic anti-cancer agent (semi-synthetic analogue of the alkaloid camptothecin). Topotecan is exerting its activity by the inhibition of the nuclear enzyme topoisomerase I that is involved in DNA replication. The inhibition is due to stabilisation of the intermediate covalent complex of enzyme and strand-cleaved DNA. As a result, DNA damage induces apoptotic cell death predominantly in replicating cells such as tumour cells.

The safety and efficacy profile of Topotecan has been demonstrated in several clinical trials, details of which can be found in the EPAR of the reference medicinal product. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this active substance.

The indication for Topotecan Hospira is different from the reference medicinal product. It is part of the indication approved for the reference medicinal product.

Topotecan Hospira concentrate for solution for infusion is indicated (as monotherapy) for treatment of patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate. Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination.

Hycamtin powder for concentrate for solution for infusion is indicated (as monotherapy) for the treatment of:

- Patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.
- Patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate.

Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix which is recurrent after radiotherapy, and for patients with Stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment-free interval to justify treatment with the combination.

2.2 Quality aspects

Introduction

Topotecan Hospira Concentrate for Solution for Infusion is available in a single presentation of 4mg/4ml. It is supplied in a 5 ml glass vial containing 4mg of topotecan (as the hydrochloride salt).
The bulk product is a solution of topotecan hydrochloride in Water for Injections.
Tartaric acid is used to maintain the pH of the solution within the target range, and hydrochloric acid and sodium hydroxide are used to adjust the bulk solution prior to filling.

It is presented in clear Type I glass vials. The vials are closed with chlorobutyl rubber closures and aluminum seals with plastic flip-off tops. The final sealed, labeled vial may also be sheathed with a clear protective plastic sleeve.

Active Substance

Topotecan hydrochloride is a yellow to orange powder. The molecule has one chiral centre and its chemical name is (S)-10-[(Dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride.
The chemical structure is characterised by several physicochemical studies such as elemental analysis, Ultraviolet (UV), Infrared (IR), Mass Spectrometry (MS) and Nuclear Magnetic Resonance (NMR).
The crystal form of topotecan hydrochloride is very sensitive to the recrystallisation conditions and this compound is polymorphous. The polymorphism of topotecan hydrochloride has been suitably studied and XRPD patterns show that the same crystalline form is consistently obtained in the GMP batches and in the in-house reference standard.

- Manufacture:

Topotecan hydrochloride is synthesised by a two-step process (one chemical reaction followed by a salt formation). Detailed information about the manufacturing process, process validation and control of critical manufacturing steps has been supplied in the form of an Active Substance Master File. At the time of the opinion, only one active substance manufacturer is authorised.
Adequate in-process controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate product, starting material and reagents have been presented and are satisfactory. All relevant impurities, degradation products and residual solvents have been appropriately characterised.

- Specification:

As no monograph of topotecan exists in the Ph. Eur or USP, in-house specifications have been set for the active substance, in accordance with the principles of ICH guidelines.
The specification proposed is suitable to control the quality of the drug substance manufactured using the current process and includes: appearance, identification (HPLC and FT-IR). Assay and purity (HPLC), water content (Karl Fisher), residual solvents (GC), residual TEA (GC), heavy metals, sulphated ash, chloride content (titration), specific rotation, bacterial endotoxin, microcount and x-ray powder diffraction.
The analytical methods used in routine controls are correctly described and have been correctly validated following the ICH Q2 (R1) guideline. All validation parameters are correctly determined and comply with their acceptance criteria.
Batch analysis (n=3) data have been presented and all batches were in compliance with the proposed specification.

- Stability:

The manufacturer has conducted stability studies at long-term (5±3ºC) during 18 months and accelerated conditions (25±2ºC/60±5% RH) during 6 months on two batches. Additionally, forced degradation studies and solid state stressed studies have been performed.
Parameters tested included: appearance, assay and purity by HPLC and water content by Karl-Fisher. The test methods are the same as those used in the active substance specification.

Topotecan hydrochloride is double packed in low density polyethylene (LDPE) bags before sealed in aluminium bags. Structural supports are provided by HDPE bottles/drums.

Based on the stability results, it is recommended for topotecan hydrochloride to be stored at 2-8ºC, protected from light, moisture and excessive heat. The retest period for the drug substance, stored in the proposed packaging material, is supported by the results provided.

Medicinal Product

- Pharmaceutical development:

The formulation of Topotecan Hospira was based on the innovator product Hycamtin. The objective of the pharmaceutical development was to develop a ready to use solution formulation, as an alternative to the lyophilised product Hycamtin, whilst retaining the innovator's dosing regimen and route of administration.
All excipients are widely used in parenteral products and comply with pharmacopoeial requirements.
The excipients used in the formulation are tartaric acid, water for injection and sodium hydroxide and/or hydrochloric acid. They are the same as those contained in the innovator, except for the

exclusion of mannitol. Mannitol is used in freeze-dried products as a bulking agent and as such is not required in Topotecan Hospira, a solution product.

The development activities focused on delivering a solution product, whilst ensuring stability by managing factors such as pH, temperature, oxygen exposure and maintaining topotecan in its active form while in infusion solution.

During the manufacturing process development, the possibility of terminal sterilisation was investigated and found not possible as the samples experienced significant degradation. Therefore, in accordance with the CPMP/QWP/054/98 guidance "Decision tree for the selection of sterilisation methods", the product is manufactured via a combination of aseptic filtration and aseptic processing.

The primary packaging components used for Topotecan Hospira were evaluated. The containers comply with the requirements of Ph.Eur. <3.2.1> and the closure formulation complies with the requirements of Ph.Eur. <3.2.9>. Studies have been performed to support the use of the proposed closure and container as primary packaging for Topotecan Hospira:
- the elastomeric closure has been qualified for use based on the results of biological, physicochemical, functionality and other characterisation tests.
- the suitability of the proposed closure formulation with Topotecan Hospira was investigated by studying the compatibility of the product when in contact with the closure for extended periods.
- The container closure integrity has been demonstrated by microbial challenge methods.

Compatibility studies were performed to ensure that the drug product is compatible with the diluent (0.9% Sodium Chloride and 5% Dextrose) and the container closure system.

- Adventitious agents:

Not applicable

- Manufacture of the product:

The manufacturing process can be divided in 7 steps: Compounding, Pre-filtration, Sterilising filtration, aseptic filling, complete stoppering, sealing and packaging.

The manufacturing process is considered as a non-standard process as per Annex II to Note for Guidance on Process Validation (CPMP/QWP/2054/03) but the applicant:
- Provided results of the drug product manufacturing process's validation in pilot batches
- Supported its own experience in the use of aseptic manufacturing process
Therefore, the manufacturing process will be validated according to the protocol provided on the first 3 full-scale manufacturing batches.
Adequate in-process controls are applied. No critical steps are identified, nor there are any intermediates isolated.

- Product specification

The finished product specification includes appropriate tests for appearance, identification (UV and HPLC), Colour of solution, pH, assay (HPLC), related substances (HPLC), volume in container, particulate matter, sterility and bacterial endotoxins.

Compendial methods have been verified suitable for their intended use. The non-compendial methods are perfectly described and validated in accordance with ICH Q2(R1) guideline.

Batch results were provided for 3 batches representative of the proposed commercial formula and manufacturing process. The results indicate satisfactory uniformity and compliance with the proposed specification, and that the process is under control.

- Stability of the product:

Three registration batches of the finished product packed in the intended for marketing primary packaging were put on ICH long-term (5ºC±3ºC during 12 months), and accelerated (25ºC±2ºC/60%RH during 6 months) conditions. In addition, samples were placed under intermediate (15ºC during 12 months) and stress (-20ºC during 1 month) conditions.
The following parameters were tested: appearance, colour of solution, pH, assay, related substance, particulate matters, chiral impurities, Sterility and bacterial endotoxins.

In general, the results presented support the shelf life and storage conditions as defined in the SPC.

Topotecan Hospira was diluted in two different intravenous solutions (0.9% Sodium Chloride and 5% Dextrose) at two concentrations (0.02mg/mL and 0.5mg/mL) that were stored at room temperature (25 ± 2°C) under normal light and refrigerated conditions (5 ± 3°C protected from light) for up to 24 hours. The results support the label claim regarding stability of the drug product when commixed with intravenous solutions as prescribed in the product information.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3 Non-Clinical aspects

Introduction

The Applicant submitted 27 non-clinical studies from the literature published up to February 2009. A justification why no additional studies were submitted was provided.

Pharmacology

A review of the literature which details the pharmacology of topotecan has been submitted by the Applicant.

Topotecan has been described as a water-soluble semi-synthetic derivate of natural alkaloid camptothecin. Topotecan is a selective and reversible inhibitor of topoisomerase I (TOPI), an enzyme that catalyses the cleavage and re-ligation of supercoiled DNA during replication and transcription. TOPI is essential in eukaryotic cells. The primary cytotoxic mechanism of camptothecin is replication fork collision with the stabilized TOPI cleavage complex, resulting in a double strand break, leading to cell cycle arrest and apoptosis. Topotecan is generally considered to be S-phase-specific, and cells outside of S-phase tend to be resistant to treatment.

Cell lines with low TOPI level or with altered or reduced binding of topotecan to TOPI were shown to be resistant to its cytotoxic activity. Topotecan also seems to be a substrate, although poor, for the multidrug resistance associated P-glycoprotein.

- Safety pharmacology programme

Topotecan doses of 0.25, 0.5, 2.5 and 3 mg/kg did not result in adverse CNS pharmacological effects on locomotor activity, hexobarbital sleeping time, behaviour, body temperature, electroshock response, pain response, or response to seizure-producing drugs in male CD-1 mice. Topotecan dosing caused minor (<10%) and no dose-related changes in cardiac parameters (heart rate, blood pressure and left ventricular pressure) in dogs. No dose-related biologically significant changes were noted in respiration rate or depth, blood pressure or heart rate in rats. Topotecan did not affect intestinal motility or contractility in mice and in isolated guinea pig ileum. Doses of 15 mg/m^2 in rats (10 times the clinical dose on a mg/m^2 bases) caused significant (22-34%) increases in urine volume 2-5 hours after dosing compared to the effects of saline. This increase was accompanied by changes in urinary Na^+, K^+ and Cl^-. These changes at the highest dose of topotecan tested suggested mild kidney damage, but were not considered clinically significant because of the 10-fold safety margin.

- Pharmacodynamic drug interactions

A sequence dependent interaction occurs when topotecan is used in combination with cisplatin or carboplatin, depending on whether the platinum is given on Day 1 or Day 5 of the topotecan administration. If either cisplatin or carboplatin is given with topotecan on Day 1, the dose of both drugs must be decreased to improve tolerability, compared to administration of the platinum on Day 5.

Pharmacokinetics

A review of the literature was submitted which described the pharmacokinetic aspects of topotecan.

Topotecan possesses a lactone ring that is necessary for interaction with the DNA-TOPI cleavage complex. Topotecan undergoes a pH-dependent reversible hydrolysis from the lactone form to the biologically inactive carboxylate form. In vivo, the lactone: carboxylate ratio approaches 0.5 in

dogs at 12 hours following an intravenous dose, while the AUC ratio of lactone to total topotecan in humans is approximately 35%.
Topotecan pharmacokinetics is approximately linear with dose in all species, with little evidence of accumulation following repeated doses. In mice, following a single intravenous dose of 25 mg/kg, the estimated half-lives of the lactone and total drug were 115 min and 125 min, respectively.
Topotecan rapidly distributes into tissues, and the large steady state volume of distribution (2.8 L/kg in dogs, 75 L/m^2 in humans) indicates extensive binding to tissue components. At 6 hours after dosing, no more than 1% of the dose was present in any tissue. The elimination half-life is similar across species, ranging from 50 min in rats to 100 min in dogs and 2 to 3 hours in humans. Unchanged drug also accounts for the majority excreted in urine and faeces in dogs, although the N-desmethyl derivatives of topotecan and the inactive carboxylate form accounted for 21% of the dose in dogs, and only 4% in rats. There is evidence of enterohepatic recycling in mouse and rat.
Protein binding is similar in humans, dogs and rats, ranging from 25 to 40%, with no apparent variation with drug concentration.
In nonhuman primates and in humans, the AUC of topotecan lactone has been shown to correlate with bone marrow suppression, which is the dose-limiting toxicity.

Toxicology
A review of the literature was submitted which described the toxicology aspects of topotecan. There were no toxicology studies submitted as part of the application.

- Single dose toxicity

The maximum non lethal doses (MNLD) following a single administration of topotecan to mice, rats and dogs were 40, 75 and 7.4 mg/m^2, respectively (27-fold, 50-fold, and 5-fold higher than the intended clinical dose) while the minimum lethal doses were 56, 148 and 74 mg/m^2, respectively. Target organs of toxicity were bone marrow, lymphoid tissues, gastrointestinal tract and ovaries.

- Repeat dose toxicity

Intravenous repeat dose studies of topotecan were conducted in mice (5 day study), rabbits (13 days), rats and Beagle dogs (5-28 days). An additional oral study was conducted in rats for 6 months. The dog showed the closest maximum tolerated dose (MTD) when compared to humans for an administration regimen of five daily intravenous doses (dog 1.38 mg/m^2/day; humans 1.5 mg/m^2/day). The signs of toxicity were consistent with the pharmacological effects of topotecan.
The toxicity profile was reversible and characterized by myelotoxicity (neutropenia, thrombocytopenia, lymphopenia and anaemia), lymphoid depletion, thymus atrophy and cellular depletion of the spleen at or below the maximum tolerated dose (4.7 mg/m^2/day in rats, and 1.3 mg/m^2/day in dogs; 3-fold higher and 0.9-fold the intended clinical dose, respectively). Other tissues with a rapid cell turnover, such as hair follicules and testis, exhibited degeneration and necrosis. Damage to the gastrointestinal tract was remarkably rare and only seen in the long term oral study. These observations are concordant with clinical findings.
Non-human primate (rhesus monkeys) and murine myeloid progenitors were less sensitive to topotecan than human myeloid progenitors. In contrast to mice, dog myeloid progenitors were 5-fold more susceptible to topotecan than those from humans.
Repeated dosing with topotecan caused increases in ALT and AST suggesting liver damage, although it was not confirmed histologically.

- Genotoxicity/ Carcinogenicity

Topotecan was evaluated for potential toxicity in a battery of standard tests *in vitro* and *in vivo*. Topotecan was not genotoxic in bacterial test, but it was genotoxic and clastogenic in mammalian cells as predicted by its pharmacological activity.
Long term carcinogenicity studies have not been performed. However, considering topotecan is known to be genotoxic to mammalian cells, it is a probable carcinogen.

- Reproductive and developmental toxicity

Topotecan did not show any toxic effect on male fertility in reproductive toxicity studies conducted in rats.
Topotecan administration affected early embryonic development and implantation (i.e. fetal resorption, microphtalmia, pre-implant loss, mild maternal toxicity and an increase in the number of corpora lutea) when administered to female rats at 1.36 mg/m^2/day prior to, during and post coitus.
Foetal malformations were observed in rats dosed with topotecan as well as in the control group in an embryo-foetal development study. The most frequent ones occurred in the eye (microphthalmia, anophthalmia, rosette formation of the retina, coloboma of the retina, ectopic orbit), brain (dilated lateral and third ventricles), skull and vertebrae. In rabbits, a dose of topotecan approximately equivalent to the clinical dose (1.25 mg/m^2/day) caused maternal

toxicity, anorexia, decreased litter size and embryolethality, although foetal morphology was not affected.
It was concluded that topotecan is teratogenic, embryotoxic and foetotoxic at doses less than those recommended clinically (1.5 mg/m^2/day) and therefore, topotecan may cause foetal harm in humans.

No studies were found to evaluate the toxic effects of topotecan in juvenile animals.

Lactating rats secrete topotecan into breast milk.

- Local tolerance

Topotecan intravenous or perivenous administration to dogs at 1x to 5x the concentration administered to humans revealed a level of irritation equivalent to that seen for vehicle and saline controls and consistent with minor trauma.

- Other toxicities

Immunotoxicity
Topotecan was found to be weakly antigenic following subcutaneous and intravenous administration to guinea-pigs.

- Impurities

Chemical analysis of the drug substance and the final product has identified potential impurities that may be present in Hospira´s Topotecan Injection product.
The Applicant proposed suitable release and shelf life limits for these impurities and issues of patient safety have been addressed by the literature provided.

Environmental Risk Assessment

No environmental risk assessment has been submitted..

Discussion on Non-Clinical aspects

The non-clinical studies presented by the Applicant provided an adequate overview of the pharmacological, pharmacokinetic and toxicological aspects of topotecan. There were no major issues raised during the assessment from a non-clinical point of view.

The acceptance limits established by the Applicant for impurities are in accordance with qualification thresholds established in guidelines ICH Q3A and ICH Q3B, and therefore further qualification is not required.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the lack of ERA studies is acceptable

2.4 Clinical Aspects

Introduction

The Applicant has provided a review of the literature with 35 publications dated from 1979 to 2009.

This is an application of a Generic of a Centrally Authorised Medicinal Product in accordance with Article 3(3) of Regulation (EC) No 726/2004. The Marketing Authorisation Application (MAA) for Topotecan Hospira is classified as a hybrid generic application under Article 10(3) of Directive 2001/83/EC because the pharmaceutical form of the proposed product is different from the Hycamtin reference product. Topotecan Hospira is a concentrate for solution for infusion, whereas Hycamtin is a lyophilised powder for concentrate for solution for infusion. Based on the definition of generic product of Directive 2001/83 as amended, different dosage forms of immediate release products are considered the same dosage form only if they are administered orally.

The active ingredient in Topotecan Hospira is topotecan (as topotecan hydrochloride) and it is the same with the active ingredient in Hycamtin. The strength of the Topotecan Hospira product is 4mg/4ml. This is identical to the concentration of reconstituted Hycamtin product (4 mg), when prepared for administration in 4 ml. As such, the in-use strength of the proposed and reference products is considered to be the same.

Exemption

The pharmaceutical form of Topotecan Hospira is a 'Concentrate for Solution for Infusion'. This differs from the reference product, which is a 'Powder for Concentrate for Solution for Infusion'. The Applicant developed the solution product eliminating the initial reconstitution step in the preparation of the product prior to administration. As a consequence of the change in pharmaceutical form, the formulation of the proposed and reference products is different.

Both Topotecan Hospira and reference products are administered as an intravenous infusion. The Applicant proposed that Topotecan Hospira should have part of the indication approved and, the same dosage regimen and route of administration as Hycamtin. Comparative testing has confirmed that the innovator and proposed products are pharmaceutically equivalent and have a comparable impurity profile. As the innovator and proposed products are intended for intravenous administration, bioequivalence studies are not required. Therefore no additional detailed study reports from clinical have been trials submitted by the Applicant.

Clinical studies

The Application contained clinical data from the review of the publication literature for the proposed indication:

Topotecan monotherapy is indicated for the treatment of:

Patients with relapsed small cell lung cancer [SCLC] for whom re-treatment with the first-line regimen is not considered appropriate (see section 5.1).

Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination (see section 5.1).

2.5 Pharmacovigilance

PSUR

The PSUR submission schedule should follow the PSUR schedule for the reference product.

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system version 5.3 dated November 2009 as described by the Applicant fulfils the legislative requirements.

Risk Management Plan

No description of the Risk Management Plan has to be provided by the Applicant. The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified.

Discussion on Clinical aspects

Topotecan hydrochloride has a well-recognized efficacy and an acceptable level of safety in the indications claimed for Topotecan Hospira. There were no major objections or other concerns raised during the assessment of the clinical aspects and no additional clinical studies were required.

Regarding the waiver of bioequivalence studies and/or clinical studies it is important to highlight that this product is an aqueous intravenous solution, as the reference product at the time of administration. Both products are at the same concentration at the time of administration and the excipients are similar. The absence of the mannitol as diluent for lyophilisation is irrelevant in a product for injection.
In conclusion and in accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence, Bioequivalence testing with the reference product is not required under the provisions of the Note for Guidance on the investigation of Bioequivalence and Bioavailability (CPMP/EWP/QWP/1401/98): "The Applicant is not required to submit a bioequivalence study if the

product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised product".

An RMP was considered not required as there are no safety concerns requiring additional risk minimisation activities with respect to the reference medicinal product. It was considered that routine pharmacovigilance according to the Detailed Description of Pharmacovigilance System was sufficient for safety monitoring, without the need for additional actions.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical and clinical data. A benefit/Risk balance comparable to the reference product can therefore be concluded.

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

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Topotecan Hospira in the treatment of patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate. Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix which is recurrent after radiotherapy, and for patients with Stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment-free interval to justify treatment with the combination.
Was favourable and therefore recommended the granting of the marketing authorisation.