EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 October 2011
EMA/1352/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Topotecan Eagle

International non-proprietary name: **topotecan**

Procedure No. **EMEA/H/C/002261**

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 Eagle Laboratories Ltd submitted on 30 June 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Topotecan Eagle, 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 21.12.2009.

The application concerns a hybrid medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product 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 of patients with relapsed small cell lung cancer (SCLC) for whom first line treatment with the first-line regimen is not considered appropriate.

In combination with Cisplatin 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.

The legal basis for this application refers to:

Article 10(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data and appropriate non-clinical and clinical data.

Information on paediatric requirements

Not applicable-

Information relating to orphan market exclusivity

Similarity

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

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 1mg and 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: EU/1/96/027/004, EU/1/96/027/005, EU/1/96/027/001, EU 1/96/027/003.
- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
- Product name, strength, pharmaceutical form: Hycamtin 1mg and 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: EU/1/96/027/004, EU/1/96/027/005, EU/1/96/027/001, EU 1/96/027/003.

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 Rapporteur appointed by the CHMP was:

Rapporteur: Dr.Andrea Laslop

- The application was received by the EMA on 30 June 2010.
- The procedure started on 21 July 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 08 July 2010**.**
- During the meeting on 18 November 2010, 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 19 November 2010**.**
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 March 2011
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 13 May 2011.

- During the CHMP meeting on 19 May 2011 the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant**.**
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 17 June 2011
- During the CHMP meeting on 21 September 2011 outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- The Rapporteur circulated the updated Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 20 October 2011.
- During the meeting on 20 October 2011, 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 Eagle on 20.10.2011.

2. Scientific discussion

2.1. Introduction

Topotecan hydrochloride, the active substance of "Topotecan Eagle 3 mg/ml concentrate for solution for infusion", is a cytotoxic agent. The drug substance belongs to the pharmacological class of "antineoplastic and immunomodulating agents" ATC-Code: L01XX17.

The drug product "Topotecan Eagle 3 mg/ml concentrate for solution for infusion" is designed for intravenous use only after dilution with either 0.9% w/v sodium chloride intravenous infusion or 5% w/v glucose intravenous infusion in the recommended basic solutions for infusion between 25 and 50 microgram/ml in final concentration. The pharmaceutical form of the drug product is a clear yellow to orange liquid. The vials contain 3 mg and 15mg respectively of topotecan (as hydrochloride).

Topotecan hydrochloride is a topoisomerase I inhibitor. Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents relegation of these single strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I and DNA. Mammalian cells cannot efficiently repair these double strand breaks.

The drug product is intended for the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy and for patients with relapsed small cell lung cancer 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.

The reference medicinal product is "Hycamtin 1 and 4 mg Powder for concentrate for solution for infusion" with its first authorisation on 1996-11-12. The difference compared to this reference medicinal product is a change in the pharmaceutical form, which results in the non inclusion of mannitol and tartaric acid. Topotecan Eagle is a hybrid application and it has different strength (3mg/ml) compared to the reference product. Any potential issues related to the safe handling and the administrations of the product are extensively addressed in the RMP.

Bioequivalence testing with the reference product is not required under the provisions of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) since *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*.

2.2. Quality aspects

2.2.1. Introduction

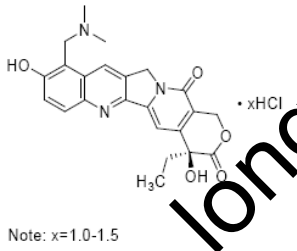
Topotecan Eagle 3mg/ml is a concentrate solution of the drug substance, topotecan hydrochloride, in water for infusion with no other excipient except hydrochloric acid used for the pH adjustment. Two volume sizes of the vial exist, a 1 ml vial and a 5 ml multi-use vial.

The vials contains 3 mg or 15mg of topotecan (as hydrochloride).The drug product is packed into type I colourless glass vials (capacity approx. 2 ml or 6 ml), with a grey butylic stopper aluminium seal and polypropylene snap-cap disk.

2.2.2. Active substance

Topotecan hydrochloride is a yellow to orange powder, it has one chiral centre originates from the starting material, 10-hydroxy-camptothecin. The active substance correspond to the (S) isomer. Topotecan hydrochloride is freely soluble in dimethyl sulfoxide and water, soluble in 0.5 % acetic acid, slightly soluble in methanol and ethanol and insoluble in acetonitrile, acetone, n-hexane, tetrahydrofuran and ethyl acetate.

The crystal form of topotecan hydrochloride is very sensitive to the re-crystallisation conditions and exhibits at least 11 polymorphs, from A to K. The LogP of topotecan hydrochloride is 2.81.



Note: x=1.0-1.5

Chemical name: (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

Manufacture

The ASMF is used for information on the drug substance. The synthesis of Topotecan hydrochloride is well described. The structure of topotecan hydrochloride has been adequately proven and its physico-chemical properties sufficiently described.

Specification

The drug substance specification include tests for appearance (visual), identification (FT-IR and HPLC), Assay (HPLC), water content (Karl Fisher), residual solvents (GC headspace), heavy metals (Ph Eur), sulphated ash (Ph Eur), specific rotation and bacterial endotoxins (Ph Eur)

Stability

Forced degradation studies/stress studies have been performed to identify the potential degradation products. The stability program of topotecan hydrochloride is designed and conducted following the ICH Q1A (R2) and EMEA Guidance on Stability Testing.

24 months stability data at long term condition, and six month at accelerated conditions for two batches were provided. No significant changes in any parameters were observed. Based on the stability data presented a justified retest period has been accepted.

2.2.3. Medicinal product

Pharmaceutical development

The aim of the pharmaceutical development was to formulate a medicinal product stable at room temperature. The topotecan HCl concentrate for solution for infusion contains 3 mg/ml of topotecan free base and presented in two fill vial presentations, 5 ml and 1 ml fill vials.

The concentrated solution meets the antimicrobial preservative effectiveness test requirements; therefore the 5 ml fill vial is for multiple dose use. The solution product should be diluted with either 0.9% Sodium Chloride Injection or 5% Dextrose Injection for infusion.

Formulation development studies confirm that topotecan is very stable in dilute hydrochloric acid solutions from 0.01 to 0.1N. Because of a pH less than 2 the product is very stable (chemically and microbiologically) and therefore results in an acceptable pharmaceutical quality. It is noted that an insoluble degradant is formed, 10-hydroxycampothecin (10-HCPT). This is a known impurity in Topotecan hydrochloride, it is well controlled in the specification and fulfils the criteria for specified impurities.

Due to a significant loss of active substance, terminal sterilization by autoclaving was unsuitable for sterilization and an alternate sterile filtration/aseptic process procedure was required. A study was conducted to select an appropriate sterilizing membrane filter compatible with a low pH solution;

Topotecan concentrate for solution for infusion will be marketed with a 5 ml fill in 6-ml vials and a 1 ml fill in 2 ml vials. The container closure systems consist of a type-I tubular flint glass vial, a butyl rubber stopper laminated with Fluoropolymer film, and an aluminium seal with a polypropylene flip-off cap.

The vials are closed with rubber stoppers and white seals.

Adventitious agents

Not applicable.

Manufacture of the product

The manufacturing methods are satisfactory described. A flow-chart of the process including in process control has been submitted.

The commercial product is manufactured in 1 ml and 5 ml presentations of identical formulation and concentration. The sterilization process is carried out through a sterile filtration/aseptic process.

The production process is performed in compliance with the principle of Good Manufacturing Practices, and it is adequately controlled by appropriate in process control tests.

Product specification

The finished product specification include appropriate test for description (visual), Clarity of solution(Ph Eur), Identification(UV, HPLC), Assay (HPLC), Related substance (ICH), pH, particulate matter (Ph Eur), Volume in container (Ph Eur), Bacterial endotoxin (Ph Eur)and sterility (Ph Eur)

Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is capable of producing finished product of the intended quality in a reproducible manner.

Stability of the product

Three registration batches of Topotecan concentrate for solution for infusion 3 mg/ml for each of the two vial presentations (1ml, 5ml), were manufactured in accordance with cGMPs and Standard Operating Procedures. Samples in the primary packaging components were placed in the stability chambers. The samples were analyzed at selected time points in accordance with the ICH requirement. 24 months stability data at long term condition for the 5ml vial and 9 month for the 1ml vials were provided. Studies at accelerated condition were also performed.

The stability results of the samples stored at accelerated and long-term conditions for Topotecan concentrate for solution for infusion are well within all parameters of the drug product specification.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

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

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.

2.3. Non- clinical aspects

2.3.1. Introduction

Topotecan Eagle 3 mg/ml concentrate for solution for infusion is a new formulation of the marketed product Hycamtin 1mg and 4 mg powder for concentrate for solution for infusion, the reference medicinal product for this submission. Hycamtin (topotecan hydrochloride), as manufactured by SmithKline Beecham plc, is available as a lyophilised injectable formulation and as an oral formulation.

Topotecan Hydrochloride Injection, as produced by Eagle, is a liquid formulation of the same active ingredient. Furthermore, it differs from Hycamtin by the absence of the inactive ingredients tartaric acid and mannitol, and by the pH.

Topotecan Eagle 3 mg/ml concentrate for solution for infusion is diluted to a final concentration between 0.012 to 0.06 mg/ml. For comparison, the fully diluted Hycamtin has a concentration of 0.01 to 0.06 mg/ml which has a pH of 3.11 to 3.58.

Although the pH of Eagle's Topotecan Hydrochloride Injection overlaps with the pH of Hycamtin (pH 3.11 to 3.58), the pH of Eagle's Topotecan Hydrochloride Injection is slightly lower. To determine any potential adverse effect of the formulation's pH at the final concentration after dilution, Eagle

Pharmaceuticals has evaluated their Topotecan Hydrochloride Injection in one in vitro and two whole animal models:

Study 700001: a rat nociception study to determine whether intraplantar injection produced behavioural responses indicative of unconscious response to painful stimuli.

Study 700002: a rabbit acute intravenous irritation study to determine whether Eagle's Topotecan Hydrochloride Injection produced adverse effects at or near the site of injection.

Study 2101: an in vitro haemolysis study to assess the potential for the low pH of Topotecan Hydrochloride Injection, as well as Hycamtin and controls, to produce adverse effects.

Comments on compliance with GLP

Studies were conducted in accordance with the V.S. Food and Drug Administration's Good Laboratory Practice Regulations 21 CFR Part 58.

2.3.2. Pharmacology

Topotecan is a semi-synthetic analogue of camptothecin that is water soluble in the lactone form and binds less strongly to plasma proteins. It undergoes a reversible, pH-dependent hydrolysis of its pharmacologically active closed-ring lactone form into an inactive hydroxycarboxylate open-ring form. The lactone form predominates at acidic pH and the carboxylate form at neutral and alkaline pH. The lactone form is a potent inhibitor of topoisomerase I.

The DNA topoisomerases are nuclear enzymes that relieve the torsional strain in supercoiled DNA by inducing reversible single strand breaks. This action enables selected regions of DNA to become sufficiently exposed and relaxed to facilitate essential cellular processes such as DNA replication, DNA repair, and transcription to occur.

Topotecan binds to the topoisomerase I-DNA complex and inhibits the induction of these single strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA.

Mammalian cells cannot efficiently repair these double strand breaks and the cells die.

Topotecan is therefore an S-phase-specific drug.

The activity of topotecan has been demonstrated in vitro and efficacy in vivo has been demonstrated in a broad range of mouse tumour models.

The synergistic effect in combination with cisplatin has been shown in vitro in a number of cell lines including those derived from human cervix uteri. In vivo this synergistic effect has been shown in an IGROV-1 tumour xenograft model.

Pharmacology Study 700001: Assessment of Nociception Following a Single Hindlimb Intraplantar Injection of EAGLE TPT in Male Rats

The objective of this study was to evaluate the potential nociceptive response following a single intraplantar injection of the test article [Eagle's Topotecan liquid concentrate (3 mg/mL); also known as SciDose TPT] or comparator article [Hycamtin] in male Sprague Dawley rats. A positive control was 5% buffered formalin.

The test article was administered once as an intraplantar injection to 2 groups (Groups 4 and 5) of Crl:CD(SD) rats at dose levels of 1.5 and 3 µg/animal. Concurrent control (Group 1), positive control (Group 2) and comparator article (Group 3) groups received the vehicle, positive control article (5% buffered formalin) and comparator article (3 µg/animal Hycamtin), respectively, on a comparable regimen. Animals were approximately 8 weeks old at the time of dose administration. Each group consisted of 5 males. The dose volume was 50 µL/animal for all groups.

Group Number	Test Article	Dose Level (µg/animal)	Dose Volume (µL/animal)	Number of Animals
1	Vehicle control	0	50	5
2	Formalin	b	50	5
3	Hycamtin	3	50	5
4	Eagle TPT	1.5	50	5
5	Eagle TPT	3	50	5
a = The vehicle control was 0.9% sodium chloride for injection, USP.				
b = A 5% formalin in sterile water for injection, USP, solution was used as the positive control article.				

Prior to dose administration on study day 0, there were no significant clinical observations noted and mean body weights were similar across all groups.

Following acute dose administration, observation of each rat was conducted by a technician who did not know the group assignment of the animals (i.e., blind). Each rat was observed for a 12-minute period immediately following dose administration.

The occurrence of paw lick and lift response was recorded for each rat over a 12-minute period (consisting of four 3-minute intervals). All animals were euthanized and discarded without macroscopic examination following completion of the 12-minute observation period.

The responses for each rat were categorized on a scale of 0 to 3 as described in the following table:

Pain Intensity Categories

0 No response (both rear paws were placed on the floor, weight was evenly distributed on both rear paws and during locomotion there was no discernible favouring of the injected paw)

1 Rat rested the injected paw lightly on the floor or on some part of its body with little or no weight placed on it paw and/or showed a slight limp during locomotion.

2 Rat elevated the injected paw to avoid contact with any surface and/or showed an obvious limp during locomotion.

3 Rat licked or bit the injected paw.

There was no pain response elicited in the test article-treated and comparator article-treated groups. However, the expected nociceptive response was exhibited in the positive control-treated animals, as evidenced by higher pain ratings during the first 9 minutes following injection when compared with the vehicle control group.

There was no indication of an aversive response to the comparator article or to either concentration of the test article through 12 minutes following subplantar injection. All animals in the comparator article- and test article-treated groups had pain ratings of 0.00 (the lowest recordable pain intensity category). The positive control article, 5% buffered formalin, exhibited the expected nociceptive response.

2.3.3. Pharmacokinetics

The pharmacokinetic properties of Topotecan are well known.

The pharmacokinetic profile of topotecan by various routes of administration has previously been evaluated in rodents (mouse and rat) and non-rodents (rabbit, dog and non-human primates).

Studies were performed in both normal and tumour-bearing animals.

As Topotecan is a widely used, well-known active substance, the applicant has not provided additional studies and further pharmacokinetic studies are not required.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity has been studied in mice, rats and dogs following intravenous administration of topotecan. The minimum lethal doses in mice, rats and dogs 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

Repeat-dose toxicity following intravenous administration of topotecan has been investigated in mice (5 days), rats (up to 1 month), rabbits (3 days19 and 19 days14) and dogs (up to 6 months). In addition, repeat dose toxicity has been studied in rats and dogs following oral administration of topotecan for up to 6 and 3 months, respectively.

It is evident that the primary dose-limiting toxicity in all these species due to topotecan treatment was myelosuppression consisting of neutropenia, thrombocytopenia, lymphopenia and anaemia. Histopathological damage associated with myelosuppression was also seen including bone marrow hypocellularity and cellular depletion of the spleen, thymus and lymph nodes. Damage to the gastrointestinal tract was rare and usually only in long-term studies of oral dosing. In some studies, repeat-dosing resulted in hepatic toxicity, characterised by increases in serum ALT and AST, and mild renal damage was inferred by transient changes in urinalysis parameters. Toxicities in these species were not progressive and were reversible.

Genotoxicity

Topotecan was not genotoxic in the bacterial reverse-mutation assay. However, as predicted based on its pharmacologic activity, genotoxic effects were observed in mammalian cells in vitro and in vivo. In the mouse in vitro lymphoma assay, topotecan caused a significant increase in the mutation frequency. Genotoxic effects were also seen in the in vitro chromosomal aberrations assay which used human peripheral blood lymphocytes. In this assay topotecan significantly elevated the number of structural chromosome aberrations. In vivo analysis in mouse bone marrow cells demonstrated that topotecan caused a significant increase in the frequency of micronucleated erythrocytes and it also decreased the polychromatic/normochromatic erythrocyte ratio indicating bone marrow toxicity. Topotecan also significantly induced chromosomal aberrations in a dose-dependent manner.

Carcinogenicity

There are no published nonclinical study data available regarding the carcinogenicity of topotecan. However, topotecan is known to be genotoxic to mammalian cells.

Reproduction toxicity

Topotecan caused embryonic and foetal death in rats and rabbits and caused significant maternal toxicity. Topotecan is therefore contraindicated in pregnant women.

In reproductive toxicity studies in rats, there was no effect on male or female fertility.

However, super-ovulation and slightly increased pre-implantation loss were observed in females.

In dogs, topotecan dosing appeared to cause an increase in the incidence of multinucleated spermatogonial giant cells in the testes.

Studies in rats suggest that topotecan and/or its metabolites are actively secreted in breast milk so breast-feeding should be discontinued at the start of therapy.

Toxicokinetic data

Not applicable

Local tolerance

As there are no published nonclinical studies available in the scientific literature regarding the local tolerance of topotecan and since the pH of Eagle's Topotecan Hydrochloride Injection in its fully diluted state, just prior to administration to patients, was slightly lower than that of Hycamtin, a local tolerance study in albino rabbits was performed:

Study Number 700002,

Title: Acute Intravenous Irritation Study of Eagle TPT in Albino Rabbits

The objective of the study was to determine the irritative potential of Eagle's Topotecan Hydrochloride Injection; following a single intravenous infusion to groups of six male albino rabbits.

Groups (each group consisted of 6 males New Zealand White rabbits)

Groups 1 and 2:	Test agents (Eagle TPT)
	dose of 0.12 mg/kg
	dose concentrations were 0.03 (Volume 4ml/kg) and
	0.06 mg/mL (Volume 2ml/kg)
Group 3	comparator test article, Hycamtin
	dose concentrations were 0.06 mg/mL (Volume 2 ml/kg)
Group 4	A positive control group
	10% glucose solution (Volume 4 ml/kg)

New Zealand White rabbits were treated with the test agents in the right ear while the left ear served as a vehicle control (0.9% saline, 4 mL/kg). Eagle TPT was administered in a single dose of 0.12 mg/kg by intravenous injection to two groups of male New Zealand White rabbits at 0.03 and 0.06 mg/mL (Groups 1 and 2). The comparator, Hycamtin, was administered at 0.06 mg/mL to Group 3 and

a positive control group (Group 4) received 10% glucose solution with its titrateable acidity adjusted to 12 mEq/L (pH 4.4).

The dose volumes were 4, 2, 2 and 4 ml/kg for Groups 1 to 4, respectively. All animals were euthanized after a 48 hour observation period.

All injection sites were examined macroscopically and microscopically.

There were no deaths, remarkable body weight changes or gross findings observed at the injection sites during necropsy. Dermal observations of slight erythema at the injection sites were noted in all groups but this included control ears injected with vehicle.

However the incidence of erythema increased for sites injected with positive control article. Microscopic changes at the injection sites included epidermal surface exudate, necrosis, ulceration, sub-epidermal degeneration, acute inflammation (phlebitis) of the marginal vein, venous thrombosis, interstitial oedema and subacute and granulomatous inflammation. The occurrence and nature of these changes were not substantially different between negative control sites and the test article treated sites. Sites administered positive control article had an increased incidence and severity of minimal to mild interstitial oedema and subepidermal degeneration.

Based on the results of this study, the irritation potential at the intravenous infusion sites in rabbits administered negative control, 0.03 or 0.06 mg/ml Eagle TPT or 0.06 mg/ml Hycamtin was comparable and considered less irritating relative to the positive control.

The Applicant, following the request of the CHMP, evaluated the local irritation potential of Topotecan Hydrochloride Injection for unintended parenteral routes of administration, (Study report : 20008606 "Acute Irritation Study of Topotecan Hydrochloride Injection by Intra-arterial Infusion and Paravenous Injection in Rabbits") as tolerance testing should be determined at sites that come into contact with the formulations as a result of the method of administration, and also at the sites that might come into contact through accidental or unavoidable exposure of the formulations, e.g. intra-arterial, or paravenous administration.

The objectives of this study were to determine the potential local irritation of Topotecan Hydrochloride Injection when given as a single dose by intra-arterial infusion and paravenous injection to rabbits, and to compare the effects of Topotecan Hydrochloride Injection to a comparator (Hycamtin). To this end, Topotecan Hydrochloride Injection or Hycamtin for Injection, diluted in 0.9 % Sodium Chloride for Injection to 0.06 mg topotecan/ml, was administered once via intra-arterial infusion (approximately 30 minutes) into the central media ear artery (with negative control article administered in a contralateral vessel) and once via paravenous injection (approximately 30 seconds) into the space surrounding the marginal ear vein (with negative control article administered in a contralateral space) to determine the potential local irritation. The study concluded that intra-arterial infusion and paravenous injection of Topotecan Hydrochloride Injection and Hycamtin, administered as a single dose, was well tolerated in rabbits at doses of 0.12 mg/kg (intra-arterial) or 0.03 mg (paravenous). Dermal irritation was noted surrounding the treatment site and was comparable among treatment groups with no biologically meaningful differences between the Topotecan Hydrochloride Injection and Hycamtin.

Other toxicity studies

To evaluate the compatibility of Eagle's Topotecan Hydrochloride Injection with blood, an in vitro study in rabbit whole blood was performed:

- Study Number 2101,

Title: Assessment of the Hemolytic Properties of Test and Reference Formulations of Topotecan Hydrochloride for Intravenous Infusion Using an In Vitro Test Method in Rabbit Whole Blood

The haemolytic properties of Eagle's Topotecan Hydrochloride Injection and Hycamtin comparator were assessed using a static, in vitro system comprised of undiluted rabbit whole blood.

Each formulation was diluted to 0.060, 0.03 and 0.012 mg/ml with saline.

An aliquot (30, 60 or 150 µL) of each formulation was added separately to 10 ml aliquots of blood. These solutions were mixed and then each split into two samples. One sample was tested immediately and the other incubated at 37°C for 30 minutes. All samples, including a vehicle blank (0.1N HCl) prepared in the same way, were centrifuged at 3000 rpm (2095 x g) for 10 minutes. Positive and negative controls consisted of whole blood prepared with water and normal saline respectively. All samples were prepared in triplicate.

The plasma supernatants were analysed by spectrophotometric detection at 540 nm for the detection of haemoglobin. The absorbance from the negative control was subtracted from the corresponding sample to correct for absorbance attributable to plasma background.

After correction for the dilution factor, the percent haemolysis was determined from a standard curve.

Results showed that the ratio of 30, 60 and 150 µL of test solution added to 10 ml of blood had little or no haemolytic impact. In all the test, reference, blank and control samples, the percent haemolysis was ≤0.5%.

2.3.5. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Topotecan Eagle manufactured by Eagle Laboratories Ltd. is considered unlikely to result in any significant increase in the combined sales volumes for all topotecan containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.6. Discussion on non-clinical aspects

The non-clinical overview provides an adequate overview of the pharmacological, pharmacokinetic and toxicological aspects of topotecan.

In general, the provided non-clinical studies are of good quality and were produced and compiled in accordance with the U.S. Food and Drug Administration's Good Laboratory Practice Regulations 21 CFR Part 58.

Regarding the difference in the pH at the final concentration after dilution, Eagle Pharmaceuticals has evaluated their Topotecan Hydrochloride Injection in one in vitro and two whole animal models. Minor issues raised during the assessment have been resolved adequately.

An environmental risk assessment is not provided as there is no expected increase in the exposure of the environment to the active substance, topotecan hydrochloride.

The CHMP agrees that no changes in the environmental risks that are not already known for topotecan, are to be anticipated for Topotecan Eagle 3 mg/ml concentrate for solution for infusion.

As the drug substance has been authorized in the EU for more than 10 years any possible risks for environment arising from use, storage and disposal of the medicinal product are covered by the instructions/measures that are included in Summary of product Characteristics.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical information provided additionally to the existing knowledge of topotecan adequately covers any issues arising from the assessment of topotecan Eagle and provided an adequate overview of the pharmacological, pharmacokinetic and toxicological aspects of topotecan.

No further amendments to the product information were needed from a preclinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Topotecan Eagle 3 mg/ml concentrate for solution for infusion containing topotecan.

The applicant adequately justifies why there is no need to generate new clinical data.

Since topotecan is administered intravenously it was not necessary to demonstrate bioequivalence. The clinical overview refers 46 publications from 1988 up to year 2010.

Therapeutic indications

Topotecan Eagle 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.

Topotecan Eagle 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.

Posology and method of administration

The recommended dosage and method of administration of the generic product Topotecan Eagle 3 mg/ml concentrate for solution for infusion is the same as that recommended for the reference medicinal product Hycamtin 1 mg/ml, from GlaxoSmithKline in the UK.

The recommended dose of Eagle's Topotecan Hydrochloride Injection, 3 mg topotecan per ml, for the treatment of patients with SCLC for whom re-treatment with the first-line regimen is not considered appropriate, is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21 day cycle. In the absence of tumour progression, a minimum of four cycles is recommended because tumour response may be delayed.

The recommended dosage, for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IV-B disease, is 0.75 mg/m^2/day of Eagle's Topotecan Hydrochloride Injection, 3 mg topotecan per ml, administered as a 30 minute intravenous infusion on days 1, 2 and 3 of each cycle. Cisplatin is administered after Eagle's Topotecan Hydrochloride Injection as an intravenous infusion on day 1 at a dosage of 50 mg/m^2/day. Treatment should be repeated every 21 days for six cycles or until disease progresses.

Pharmacological classification

Pharmacotherapeutic group: Other antineoplastic agents ATC-code: L01XX17.

Exemption

The pharmaceutical form of Topotecan Eagle 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 Eagle and reference products are administered as an intravenous infusion. Topotecan Eagle has been proposed for SCLC and carcinoma of the cervix indications. 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 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 Rev. 1):

"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".

Clinical studies

No further clinical studies have been performed with topotecan Eagle and this is considered justified (as above).

2.4.2. Pharmacokinetics

The pharmacokinetic properties of topotecan are well known.

The peak plasma concentrations and the area under the plasma concentration-versus-time curves (AUC) show linear relationship with increasing dosages. No evidence of drug accumulation is seen with daily 30-minute infusions for 5 consecutive days.

Following intravenous administration of topotecan in adults with solid tumours, at doses of 0,5 to 1,5 mg/m^2, as a 30-minute infusion, daily for five days, mean peak serum topotecan (lactone) concentration was 73 to 78 nmol/l (hydroxy acid 45 nmol/l at 20 minutes). Topotecan has a volume of distribution of approximately 130 l. Mean plasma clearance for topotecan was approximately 1,000 ml/min, with a plasma half-life of 2 to 3 hours.

The binding of topotecan to plasma proteins was low (35%) and distribution between blood cells and plasma was fairly homogeneous.

The elimination of topotecan has only been partly elucidated in humans. No recovery study with radiolabelled topotecan has been conducted.

Topotecan is rapidly eliminated from the systemic circulation. Topotecan was rapidly hydrolyzed in vivo to a less active, open-ring form. Only 20% to 35% of the total drug in plasma is found to be in the active lactone form. Elimination of the lactone form appears to result mainly from rapid hydrolysis to the caboxylate species followed by renal excretion, with 30% to 40% of the administered dose excreted in the urine within 24 hours.

Renal clearance is an important determinant of topotecan elimination.

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

2.4.3. Pharmacodynamics

The anti-tumour activity of topotecan involves the inhibition of topoisomerase I, an enzyme intimately involved in DNA replication as it relieves the torsional strain introduced ahead of the moving replication fork. Topotecan inhibits topoisomerase ¬I by stabilising the covalent complex of enzyme and strand-cleaved DNA which is an intermediate of the catalytic mechanism. The cellular sequela of inhibition of topoisomerase ¬I by topotecan is the induction of protein-associated DNA single-strand breaks. Although single strand breaks are not sufficient to produce cell death, the drug-enzyme-DNA complex ultimately results in double strand breaks. Mammalian cells cannot efficiently repair these double strand breaks and this process results in subsequent apoptosis and cell death.

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

2.4.4. Clinical efficacy

The applicant has provided an up to date review (with 46 publications from 1988 to 2010) of the current state of knowledge concerning the clinical use of topotecan in the following claimed indications:.

Small Cell Lung Cancer (SCLC)

The marketing authorisation for Hycamtin as a monotherapy for patients with relapsed SCLC for whom re-treatment with the first-line regimen is not considered appropriate was granted by the European Medicines Agency (EMEA) on 1 February 2006 for intravenous (i.v.) therapy.

The efficacy and safety of topotecan in patients with recurrent SCLC have been demonstrated in a number of Phase II studies. These studies demonstrated a higher response rate and prolonged median survival in chemosensitive compared to chemorefractory SCLC. Topotecan has produced overall response rates (ORRs) of 14 to 38% in chemotherapy-sensitive SCLC and 2 to 11% in chemotherapy-resistant SCLC, with an additional 20 to 36% of patients developing stable disease (SD).

Findings from these studies were confirmed in a randomized, multicentre, phase III trial conducted by von Pawel et al of topotecan versus cyclophosphamide, doxorubicin and vincristine (CAV) combination chemotherapy regimen.

The results of this large randomized controlled trial indicate that topotecan used, as a single agent, is at least as efficient as the combination chemotherapy regimen CAV in the treatment of patients with recurrent SCLC. Regarding safety, topotecan showed some clinical benefit in improving quality-of-life in patients with recurrent small-cell lung cancer, resulted in improved palliation of several symptoms, including dyspnoea, anorexia, fatigue, hoarseness and interference with daily activities.

Carcinoma of the cervix

Topotecan in combination with cisplatin, is indicated for treatment of patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IV-B disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment in combination. The marketing authorisation for Hycamtin in combination with cisplatin, in this indication was granted by the EMEA for intravenous therapy on 22 November 2006.

Multiple combination regimens have been studied in patients with advanced disease.

Cisplatin has proven to be the most effective single cytotoxic agent for the treatment of advanced or recurrent cervical cancer. However, the response rate is about 23%, and most of the responses are

brief. Hence, more effective chemotherapeutic strategies for this disease are clearly needed. Topotecan and cisplatin combination have produced higher survival and progressive free survival rates in the management of these patients.

A statistically significant survival advantage for cisplatin in combination with topotecan over cisplatin alone in women with Stage IV-B recurrent cervical cancer has been demonstrated in an open-label, randomised, prospective Phase III trial.

As chemotherapy in this setting is considered palliative, quality of life (QoL) assessments were incorporated into the trials endpoints. Despite the significantly higher incidence of toxicity in the combined cisplatin/topotecan arm, there was no perceived difference in QoL compared with cisplatin alone.

Together these data demonstrate that topotecan improves response rate, progression-free survival and overall survival when added to cisplatin in treating metastatic and recurrent cervical cancer.

Regarding safety, topotecan in combination with cisplatin is well-tolerated although myelosuppression is greater than with the individual agents alone. When topotecan is used in conjunction with cisplatin at doses at or below 50 mg/m^2 resulting neutropenia is both reversible and non-cumulative.

As summarised above, topotecan hydrochloride has a well-recognized efficacy and an acceptable level of safety in the indications claimed for Topotecan Eagle and no additional clinical studies are needed.

Topotecan Eagle 3 mg/ml concentrate for solution for infusion is a new formulation of the marketed product Hycamtin 1mg and 4 mg powder for concentrate for solution for infusion, the reference medicinal product for this submission.

The rationale for the development of this formulation was based on the advantage compared to the reference medicinal product Hycamtin that for Topotecan Eagle no additional reconstitution step is needed, and therefore Eagle's Topotecan is easier to use than the originator product and assures safer handling for personnel (pharmacists, nurses and clinicians). Another advantage is the "multiple-use 6 ml glass vials". As the product is self-preserving, and any remaining product in the vial can be used over several days, wastage is therefore eliminated.

Furthermore, Topotecan Eagle 3 mg/ml concentrate for solution for infusion differs from Hycamtin by the absence of inactive ingredients tartaric acid and mannitol, and by the pH.

The proposed dosage regimens are identical to those currently registered for the originator product. Eagle's Topotecan Hydrochloride Injection, 3 mg/ml, is a concentrated solution. Just like the reference medicinal product, it is to be diluted with either 0.9% Sodium Chloride Injection or 5% Dextrose Injection prior to infusion. It is diluted to a final concentration between 0.01 to 0.06 mg/ml. For comparison, the fully diluted Hycamtin has a concentration of 0.01 to 0.06 mg/ml which has a pH of 3.11 to 3.52.

Topotecan Eagle 3 mg/ml concentrate for solution for infusion meets the requirements on safety and efficacy for a marketing authorisation application under Article 10(3) "hybrid", and no further data are required.

Additional data

None

Post marketing experience

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

2.4.5. Clinical safety

The clinical safety of the reference product is well documented. Topotecan hydrochloride has an acceptable level of safety in the indications claimed and no additional clinical studies are needed.

Topotecan is generally well tolerated. The dose-limiting toxicity of topotecan is myelosuppression consisting of neutropenia, thrombocytopenia, neutropenic fever and anaemia. Neutropenia is noncumulative and reversible. Myelosuppression can be managed by dose reductions, treatment delays and granlocyte colony stimulating factor (G-CSF) administration. Non-haematological adverse effects are generally mild and include nausea, vomiting, rashes, fatigue, diarrhoea and alopecia.

However, the proposed product has a higher concentration (3 mg/ml) than the currently available topotecan products on the market. Consequently, there is an important risk of medication error during product preparation and dilution which may result in patients receiving an overdose with potentially serious and life-threatening consequences.

Measures to eliminate / reduce the risk of medication errors are discussed with the CHMP and are in place by the Applicant. These measures include warning statements in the labelling, dilution instructions, boxed warnings in the product information, a unique vial collar and educational material agreed with the CHMP.

2.4.6. Post marketing experience

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

2.4.7. Discussion on clinical aspects

Topotecan is a cytotoxic anti-cancer agent, a semisynthetic 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.

Bioequivalence testing with the reference product is not required under the provisions of the "Guideline on the investigation of Bioequivalence" (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".

There are currently several versions of topotecan for intravenous use available for use in the EU, presented as powder for reconstitution and dilution or as concentrate for dilution, as either 1 mg/ml or 4 mg/ml vials.

Topotecan Eagle concentrate contains 3 mg/ml of topotecan, which is a higher initial concentration than found in other topotecan products for intravenous infusion.

Topotecan Eagle presents some practical advantages such as being a liquid formulation without the need for reconstitution, its ease of administration and storage at room temperature.

There are no concerns with Topotecan Eagle from a clinical efficacy point of view.

However, the difference in the strength of the product before the preparation of solution for infusion poses a risk of medication error and is discussed in detail below. The Applicant introduced a number of measures agreed with the CHMP to minimize the risk of medication errors.

2.4.8. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of topotecan hydrochloride was provided and in accordance with the relevant guideline, no additional clinical studies were considered necessary.

However, the proposed product has a higher concentration (3 mg/ml) than the currently available topotecan products on the market. Consequently, there is an important risk of medication error during product preparation and dilution which may result in patients receiving an overdose.

Due to the proposed risk minimisation measures, it is expected that the risk of medication errors will be low. If a medication error occurs on a single dosing day, the consequences are predictable and manageable and the overdose given will be within the dose range previously tested in published efficacy and safety studies of topotecan. In principle, this seems to be supported by the published literature.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative 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.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

SUMMARY OF THE RISK MANAGEMENT PLAN:

Safety issue	Agreed Pharmacovigilance activities	Agreed risk minimisation activities
Identified Risks:		
Medication Error	Routine pharmacovigilance with specific query for cases where symptoms and signs of overdose have occurred to determine if medication error has occurred.	Specific statements regarding difference in concentration in vials of Topotecan Eagle compared to other topotecan products and the need to appropriately dilute the product before use – in Sections 4.2, 4.4 and 6.6 of the SPC. Vial collar to act as strong visual reminder to notice the concentration. Communication Plan to ensure healthcare professionals and pharmacies using oncology agents are aware of the key messages regarding different concentration, notice

Safety issue	Agreed Pharmacovigilance activities	Agreed risk minimisation activities
		concentration and risk of medication error with potentially life-threatening overdose. The effectiveness of the Communication Plan will be tested.
Diarrhoea	Routine pharmacovigilance via spontaneous ADR reporting with 6-monthly initial PSUR schedule.	The frequency and severity of diarrhoea is given in SPC Section 4.8 - Undesirable Effects and also in the PIL under Possible Side Effects.
Bone marrow suppression	Routine pharmacovigilance via spontaneous ADR reporting with 6-monthly initial PSUR schedule.	There is a contraindication in SPC Section 4.3, Contraindications: "..already have severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils < 1.5 x 10^9/l and/or a platelet count of < 100 x 10^9/l The frequency and severity of neutropenia, anaemia, and thrombocytopenia and their management are given and discussed in the following sections of the SPC: Section 4.2 – Posology and Method of Administration Section 4.4 – Special Warnings and Precautions for Use Section 4.8 – Undesirable Effects Manifestations of bone marrow suppression are also given in the PIL under Possible Side Effects.
Neutropenic colitis	Routine pharmacovigilance via spontaneous ADR reporting with 6-monthly initial PSUR schedule.	That topotecan-induced neutropenia can cause neutropenic colitis, which may be fatal is given in SPC Section 4.4 – Special Warnings and Precautions for Use., and also given as a side effect in Section 4.8 – Undesirable Effects. Manifestations of neutropenic colitis are given in the PIL under Possible Side Effects.
Infection	Routine pharmacovigilance via spontaneous ADR reporting with 6-monthly initial PSUR schedule.	The frequency and severity of infection together with progression to sepsis, which may be fatal is given in SPC Section 4.8 – Undesirable Effects and also given in the PIL under Possible Side Effects.
Interstitial lung disease	Routine pharmacovigilance via spontaneous ADR reporting with 6-monthly initial PSUR schedule.	The fact that topotecan has been associated with reports of interstitial lung disease, some of which resulted in fatality is given in SPC Section 4.4 - Special Warnings and Precautions and given as a side effect in

Safety issue	Agreed Pharmacovigilance activities	Agreed risk minimisation activities
		Section 4.8 – Undesirable Effects. The possibility of interstitial lung disease is given in the PIL under Take Special Care with Topotecan Eagle and also under Possible Side Effects.
Fatigue	Routine pharmacovigilance via spontaneous ADR reporting with 6-monthly initial PSUR schedule.	The frequency and severity of fatigue is given in SPC Section 4.8 – Undesirable Effects and also in the PIL under Possible Side Effects.
Alopecia	Routine pharmacovigilance via spontaneous ADR reporting with 6-monthly initial PSUR schedule.	The frequency and severity of alopecia is given in SPC Section 4.8 – Undesirable Effects and also in the PIL under Possible Side Effects.
Anorexia	Routine pharmacovigilance via spontaneous ADR reporting with 6-monthly initial PSUR schedule.	The frequency and severity of anorexia is given in SPC Section 4.8 – Undesirable Effects and also in the PIL under Possible Side Effects.
Potential Risks:		
Pregnancy (risk of exposure *in utero*)	Routine pharmacovigilance via spontaneous ADR reporting with 6-monthly initial PSUR schedule.	SPC: 4.6 Fertility, pregnancy and lactation <u>Contraception in males and females</u> As with all cytotoxic chemotherapy, effective contraceptive methods must be advised when either partner is treated with topotecan. <u>Women of childbearing potential</u> Topotecan has been shown to cause embryo-foetal lethality and malformations in preclinical studies (see section 5.3). As with other cytotoxic medicinal products, topotecan may cause foetal harm and therefore women of childbearing potential should be advised to avoid becoming pregnant during therapy with topotecan. <u>Pregnancy</u> If topotecan is used during pregnancy, or if the patient becomes pregnant during therapy with topotecan, the patient must be warned of the potential hazards to the foetus. PIL: Pregnancy and breast-feeding Topotecan Eagle should not be used during pregnancy, unless clearly necessary. If you

Safety issue	Agreed Pharmacovigilance activities	Agreed risk minimisation activities
		are pregnant or think you might be pregnant, tell your doctor immediately. Women who could get pregnant should use contraception to stop them getting pregnant during treatment. Men having Topotecan Eagle who wish to father a child should ask their doctor for family planning advice.
Interactions with BRCP and P-gp inhibitors, cyclosporine A, and platinum	Routine pharmacovigilance via spontaneous ADR reporting with 6-monthly initial PSUR schedule.	SPC: 4.5 Interaction with other medicinal products and other forms of interaction In combining topotecan with other chemotherapy agents, reduction of the doses of each medicinal product may be required to improve tolerability. However, in combining with platinum agents, there is a distinct sequence-dependent interaction depending on whether the platinum agent is given on day 1 or 5 of the topotecan dosing. If either cisplatin or carboplatin is given on day 1 of the topotecan dosing, a lower dose of each agent must be given to improve tolerability compared to the dose of each agent which can be given if the platinum agent is given on day 5 of the topotecan dosing. When topotecan (0.75 mg/m^2/day for five consecutive days) and cisplatin (60 mg/m^2/day on Day 1) were administered in 13 patients with ovarian cancer, a slight increase in AUC (12 %, n = 9) and C_{max} (23 %, n = 11) was noted on day 5. This increase is considered unlikely to be of clinical relevance. Note: Information regarding the potential risk of interactions with BRCP and P-gp inhibitors, as well as cyclosporine A is currently only included in the SPC for the oral presnentation of the reference product, Hycamtin and not for intravenous topotecan. Therefore, it is not proposed in the Topotecan Eagle SPC.
Missing Information:		
Use in subjects with renal failure	Routine pharmacovigilance via spontaneous ADR reporting	Dosage recommendations in renally impaired patients are given in SPC Section 4.2 Posology

Safety issue	Agreed Pharmacovigilance activities	Agreed risk minimisation activities
	with 6-monthly initial PSUR schedule.	and Method of Administration. A warning stating there is insufficient information in patients with severely impaired renal function is given in Section 4.4 Special Warnings and Precautions for Use. The pharmacokinetics of topotecan in patients with renal impairment is described in Section 5.2 Pharmacokinetic Properties.

The listing of important identified and potential risks as well as missing information is in accordance with the listing included in the EU-RMP of the reference product Hycamtin which is currently authorised as 1 mg and 4 mg powder for concentrate for solution for infusion, and also as 0.25 mg and 1 mg hard capsules. However the EU-RMP exists only for the oral formulation (0.25 mg and 1.0 mg capsules). No additional risk minimisation activities are proposed for these oral formulations beyond the presentation of risks in the Product Information and routine pharmacovigilance activities.

In comparison to the EU-RMP of the reference product, the EU-RMP for Topotecan Eagle has been amended with the risk of medication errors resulting in overdose due to the different strength of Topotecan Eagle, which is unique when compared to other topotecan products in the European market. The potential risk of overdose which is included in the EU-RMP of the reference product Hycamtin is covered by the identified risk of medication error in the EU-RMP of Topotecan Eagle.

Although no cases concerning medication errors with Topotecan Eagle have been reported so far, it is acceptable to classify medication errors as important identified risk, as topotecan was the third most common drug where medication errors occurred according to a published study which examined the errors in prescriptions of antineoplastic agents.

In order to minimise the risk of medication error the Applicant has implemented bolded, black boxed statements in SmPCs and PILs introduced by "Concentration must be noticed or life-threatening overdose may occur". The same information appears on the outer packaging. Each vial receives a vial ring collar with the information "Caution: notice concentration 3 mg/ml", respectively "Caution: notice concentration 15 mg/5ml (3 mg/ml)." Furthermore tables, which provide precise instructions for dilution, have been included in the SmPC as well as in the PL (information for medical or healthcare professionals).

The objective of the "Communication Plan" is to alert and educate healthcare professionals and hospital pharmacies dealing with oncology agents about the different concentration with Topotecan Eagle and to increase awareness of the potential for medication errors due to confusion with other topotecan products.

The audience is healthcare professionals and hospital pharmacies dealing with oncology agents. The SmPC will be distributed via usual means (mail shot, sales force, on MAH web site). A safety information Communication letter will be issued prior to marketing. The need and timing of follow-up reminder Safety information Communication letters, as well as distribution of these letters will be discussed and agreed prior to launch with each concerned National Competent Authority. The purpose of the communication is to alert to difference in concentration and risk of medication errors with potential life-threatening consequences, to draw attention to vial collar as visual reminder (must not be removed at any time), to inform of anticipated effects of overdose (e.g. bone marrow suppression) and

also to encourage reporting of actual medication errors and any safety events that might be a consequence of a medication error – ADR form included in the Safety Information Communication letter for this purpose.

The Communication Plan, as currently proposed by the Applicant in the EU-RMP for Topotecan Eagle, is acceptable.

The EMA/CHMP consulted different health care professional organisations such us The European Association of Hospital Pharmacists and The European Oncology Nursing Society in order to know how the different strength of Topotecan Eagle 3mg/ml could cause medication errors and/or be confusing for health care professionals when preparing the product to be administered.

Considering the concerns discussed and the feedback received from consultation with Healthcare professional Organisations, the following additional risk minimisation activities were required:

The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to use and/or prescribe Topotecan Eagle are provided with a Safety Information Communication.

In summary, the Safety Information Communication should contain the following:

- The risk of medication error due to the higher concentration than the dilution concentration of the originator, with potentially life-threatening consequences.
- Reference to the vial collar as visual reminder of this difference and the instruction that it must not be removed at any time.
- The anticipated effects of overdose (e.g. bone marrow suppression).
- An encouragement of reporting of actual medication errors and any safety events that might be a consequence of a medication error.
- A form to report medication errors.

PSUR submission

The PSUR cycle for the medicinal product should follow a half-yearly cycle until otherwise agreed by the CHMP.

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.

Furthermore, as part of the Risk minimisation measures and as a way to verify the success of the proposed "Communication Plan", a testing will be conducted prior to first market launch, and 6 months after market launch in the top 5 countries by prescription volume.

A total of 10 healthcare professionals (physicians, oncology nurses, pharmacists) who are routinely preparing oncology agents for intravenous administration will be identified in each of the countries.

A structured test will be conducted on the SPC, the instructions given in the PL section "The following information is intended for medical or healthcare professionals only", and the labelling using the actual cartons and vials. A different set of participants will be used for each test. Each participant will be given either the SPC, the PIL, or the carton/vial for Topotecan Eagle. A series of questions will be developed aimed at testing each participant's understanding of the totality of the labelling and packaging with a focus on the higher concentration compared to other topotecan products, the risk of medication errors and overdose, and the preparation and dilution instructions in the SPC. In addition, testing will check on understanding of the following: the "opened on" field on the vial label for the

15 mg/5 ml vial and carton, and instructions for sterile handling and storage, including storage times and conditions for the 15 mg/5 ml vial after first use. For re-testing, a fresh set of participants for each test will be used.

3. Benefit-risk balance

The application contains adequate quality and non clinical data and sufficient clinical data from published literature. Bioequivalence testing with the reference product is not required under the provisions of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98/Rev1) since 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

A benefit/Risk balance comparable to the reference product Hycamtin 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 additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Topotecan Eagle 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. (as monotherapy)
- (in combination with cisplatin) 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

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSUR cycle

The PSUR cycle for the medicinal product should follow a half-yearly cycle until otherwise agreed by the CHMP.

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

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of a Safety Information Communication with the national competent authority, including the need and the timing of any follow-up Safety Communication Information, as well as the distribution list of such Information.

The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to use and/or prescribe Topotecan Eagle are provided with a Safety Information Communication.

The Safety Information Communication should contain the following:

- The risk of medication error due to the higher concentration than the dilution concentration of the originator, with potentially life-threatening consequences.
- Reference to the vial collar as visual reminder of this difference and the instruction that it must not be removed at any time.
- The anticipated effects of overdose (e.g. bone marrow suppression).
- An encouragement of reporting of actual medication errors and any safety events that might be a consequence of a medication error.
- A form to report medication errors

Obligation to complete post-authorisation measures

Not applicable

Specific obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

Not applicable

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

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of a Safety Information Communication with the national competent authority,

including the need and the timing of any follow-up Safety Communication Information, as well as the distribution list of such Information.

The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to use and/or prescribe Topotecan Eagle are provided with a Safety Information Communication.

The Safety Information Communication should contain the following:

- The risk of medication error due to the higher concentration than the dilution concentration of the originator, with potentially life-threatening consequences.
- Reference to the vial collar as visual reminder of this difference and the instruction that it must not be removed at any time.
- The anticipated effects of overdose (e.g. bone marrow suppression).
- An encouragement of reporting of actual medication errors and any safety events that might be a consequence of a medication error.
- A form to report medication errors