European Medicines Agency
Evaluation of Medicines for Human Use

ASSESSMENT REPORT

FOR

TOPOTECAN TEVA

International Non-proprietary Name: topotecan

Procedure No. EMEA/H/C/001071

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 Teva Pharma B.V. submitted on 30 September 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Topotecan Teva, 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).

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: (dd-mm-yyyy) **1996-11-12**
- Marketing authorisation granted by:
  - Community
- (Community) Marketing authorisation number:

1 mg vials: 5 vials EU/1/96/027/004
1 vial EU/1/96/027/005
4 mg vials: - 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:

- Product name, strength, and pharmaceutical form: Hycamtin 1mg and 4mg powder for concentrate for solution for infusion

- Marketing authorisation holder: **SmithKline Beecham plc**
- Date of authorisation: (dd-mm-yyyy) **1996-11-12**
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1 vial EU/1/96/027/003

The Rapporteur appointed by the CHMP and the evaluation team were:

Rapporteur : Andrea Laslop

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 30 September 2008.
- The procedure started on 22 October 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 January 2009.
- During the meeting on 16 - 19 February 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 19 February 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 April 2009.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 05 June 2009.
- During the meeting on 22 – 25 June 2009, 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 Teva on 25 June 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Topotecan hydrochloride is a chemotherapy agent. The active substance belongs to the pharmacological class of “antineoplastic and immunomodulating agents” ATC-Code: L01XX17. The medicinal product “Topotecan Teva 1 mg/1 ml and 4 mg/4 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.

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 medicinal 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 12 November 1996. The difference compared to this reference medicinal product is a change in the pharmaceutical form, which results in the non inclusion of Mannitol.

2.2 Quality aspects

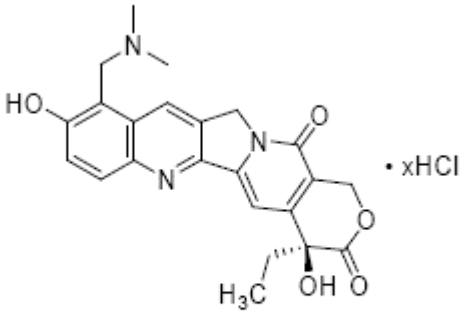
Introduction

The medicinal product is a clear, pale yellow liquid. The vials contain 1 mg topotecan (as hydrochloride) or 4 mg topotecan (as hydrochloride), respectively. A recommended overfill is used because of the excess of volume (1 ml: 1.1 ml respectively 4 ml: 4.25 ml).
The medicinal product is packed into type I colourless glass vials (capacity approx. 4 ml or 10 ml), with a bromobutyl stopper and a metallic cap with a coloured polypropylene disk.

Active Substance

The information on the active substance topotecan hydrochloride is presented in form of an Active Substance Master File with an open and a restricted part.

Topotecan hydrochloride (INN) as described below is a yellow to orange powder. It possessed one chiral centre originating from the starting material and the manufacturing process does not alter this chirality.
Physico-chemical properties including parameters such as solubility, pH, pKa, polymorphism, partition coefficient and melting point have been adequately studied. Topotecan hydrochloride is hygroscopic.
The crystal form of topotecan hydrochloride is very sensitive to the re-crystallisation conditions and although it exhibits several possible polymorphs, only one polymorph was obtained and adequately controlled through the manufacturing process.



Note: x=1.0-1.5

- **Manufacture**

Topotecan hydrochloride is synthesised in two chemical steps: 1 chemical reaction followed by salt formation, and subsequent purification.
The route of synthesis is described in the open part but the details were provided in the restricted part of the ASMF. This has been assessed and was found satisfactory.

The structure of Topotecan hydrochloride has been fully elucidated including techniques such as Powder Diffractometry (control of polymorph, X-ray), Elemental Analysis, Ultraviolet (UV), Infrared (IR), Mass Spectrometry (MS) and Nuclear Magnetic Resonance (^{1}H-NMR, ^{13}C-NMR).

Discussion about impurities, including organic impurities, inorganic impurities and residual solvents has been presented. Impurities are well controlled in the active substance and limits are in line with ICH Q3Aand ICH Q3C guidelines.

- **Specification**

The active ingredient is tested according to in-house specification as a pharmacopoeial monograph is not available yet. Appropriate specifications from the ASMF holder and from Teva have been presented and include parameters such as appearance, identification (IR and HPLC), assay and impurities (HPLC), water content (Karl-Fischer) residual solvents (GC), heavy metals, residue on ignition, specific rotation, chloride content, bacterial endotoxins, and microbial quality.
Analytical methods used for the control of active substance have been fully described and validated adequately validated in accordance with ICH guideline Q2.
Results from two batches analysed against both specifications were found satisfactory.

Topotecan hydrochloride is double packed in low density polyethylene (LDPE) bags ensuring sufficient protection against light and moisture. The package bags are sealed with twist ties before inserted into aluminium foil bags that do not contact with the product. Structural support is provided by HDPE bottles/drums. The packaging materials comply with PhEur. requirements. Satisfactory IR identification and certificates of analysis have been provided.

- **Stability**

The stability program of topotecan hydrochloride is designed and conducted following the guideline ICH Q1A (R2) and EMEA Guidance on Stability Testing.
Parameters tested included appearance, assay and purity and water content. Analytical testing methods for stability are the same as those used in the testing of topotecan hydrochloride.

Stability studies have been carried out on two batches under long term and accelerated conditions (18 months at (5 ± 3°C) and 6 months (25 ± 2°C / 60 ± 5% RH) are provided. Long-term testing (5 ± 3°C) is scheduled until 60 months. Studies will be updated when results become available.

No obvious degradation is observed from the current stability data.

Additionally, Forced degradation studies have been performed to identify the potential degradation products. Stability results showed that the active substance was unstable under oxidation condition, light, basic or aqueous solutions. Based on these results, a re-test period of 24 months can be granted when stored at 2 - 8 °C, protected from light, moisture and excessive heat.

Medicinal Product

Topotecan Teva 1 mg/ml concentrate for solution for infusion is a pale yellow solution. It is supplied in vials as a sterile, preservative-free solution intended for dilution with 5% glucose solution or 0.9% sodium chloride prior to intravenous infusion. The product is available in 1 mg/1 ml and 4 mg/4 ml single use vials.
The formulation of this product is based on the reconstituted lyophilized product Hycamtin, manufactured by the innovator GlaxoSmithKline.
The container closure consists of 1 ml colourless PhEur. type I glass vials (1 ml or 4 ml) closed by a bromobutylstopper capped with aluminium seal with a propylene cover.

- **Pharmaceutical Development**

The objective of the pharmaceutical development was to obtain a formulation of Topotecan 1 mg/ml concentrate for solution for infusion, 1 and 4 ml. Except for the presence of mannitol, the formulation is identical to the formulation of the reconstituted lyophilized innovator's product Hycamtin, GlaxoSmithKline. Mannitol in Hycamtin is used as a bulking agent to obtain a nice cake after lyophilization. The absence of mannitol in this product will not influence the solution as administered to the patient.

The pharmaceutical development including the choice of the active substance and the excipients was adequately described. The excipients used in the formulation are all compendial excipients that are commonly used in this type of formulation. Tartaric acid is added to solutions for injection as a stabilizer to maintain aqueous solubility. NaOH/HCl are used to adjust the pH if needed.Water for injection is widely used as solvent in the pharmaceutical preparations. The excipients used are Ph.Eur. grade. All methods are compendial methods and are therefore considered validated. Because the product is intended for parenteral use, microbial count and bacterial endotoxin test will be performed for the excipients. Certificates of analysis issued by the applicant and by the manufacturers of the excipients are included.

Standard manufacturing methods and processes were used to obtain the product. No overage was used during the preparation of the concentrate. Adequate in-process controls have been performed.

Compatibility studies were performed to simulate the contact of Topotecan 1 mg/ml bulk solution during the manufacturing process with laminated bags and stainless steel collecting vessels are used as holding material to store the filtered bulk solution prior to filling it into vials

Sterilisation has been performed by aseptic filtration through sterilising grade 0.2 µm membrane filters and the solution was aseptically filled in vials and closed with stoppers and snap caps. The medicinal product manufacture provided adequate justification that terminal sterilisation was not possible because of degradation of the active substance and that aseptic processing was the method of choice in accordance with the "Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)"

The primary packaging materials selected are standard packaging materials used routinely for parenteral preparations. Stability studies have proven that the selected quality of the closure system is suitable for the intended use.
Furthermore, an investigation has been carried out with respect to extractables from the rubber stoppers. From the results of the investigations it can be concluded that the rubber stopper formulation is compatible with the medicinal product.

- **Adventitious Agents**

Not applicable

- **Manufacture of the Product**

The manufacturing process can be divided in 4 main steps: preparation of the bulk solution, sterile filtration, aseptic filling, followed closing the vials and packaging.
The manufacturing process is described in detail. All relevant and critical steps are controlled and appropriate in-process controls have been set up.

For process validation purpose data of four stability batches (pilot and production batches) using the production facility and equipment are available. Based on the presented results, it can be concluded that the manufacturing process of Topotecan Teva 1 mg/ml, concentrate for solution for infusion is robust and well controlled and produces a uniform product and therefore is considered validated

- **Product Specification**

The finished product specifications at release and shelf-life include the following criteria: appearance (visual), identification of active substance (UV and HPLC), colour of solution (PhEur), visible particles (PhEur), closure integrity (visual), extractable volume (PhEur), subvisible particles (PhEur), pH (PhEur), related substances (HPLC), assay of topotecan (HPLC), sterility (PhEur), bacterial endotoxins (PhEur).

Analytical methods used were all Ph.Eur.-methods, except the methods used for the assay of topotecan and related substances. Methods were described and validated in accordance with the provisions of the ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology.

Batch results were provided for 4 batches (pilot and production-scale) on each manufacturing site (8 batches in total), and all results were found in compliance with the proposed specifications.

- **Stability of the Product**

Two production batches of each volume (1 ml and 4 ml) kept in the commercial packaging have been placed under ICH long-term and accelerated conditions (12 months at 5 °C ± 3 °C and 6 months at 25 °C ± 2 °C/60% RH . Also 6 months stability data were provided from batches obtained from another manufacturing site.
The shelf-life specifications include the same parameters and tests as the release specifications testing. In all cases the stability results presented were satisfactory and support the shelf life and storage conditions as defined in the SPC.

The photostability data for the medicinal product in the primary packaging show degradation products and a decrease of the topotecan hydrochloride content and therefore the product will be protected from light (secondary packaging).

Stability studies were also conducted on two batches where the product was diluted with 0.9% sodium chloride for injection or 5% glucose for injection into concentrations of 0.05 mg/mL to 0.025 mg/mL in non PVC infusion bags. Data showed that infusion mixtures can be kept for 72 hours in a refrigerator (2 - 8 °C) or at room temperature (about 15 - 25 °C and ambient light).

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and medicinal 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

There were no detailed non-clinical pharmacology, pharmacokinetics and toxicology study reports submitted by the applicant. The non-clinical studies refer to 28 publications from 1993 to 2008. The applicant submitted a justification why no additional studies are required.

Pharmacology

A review of the literature has been submitted by the applicant which details the pharmacology of topotecan. Topotecan hydrochloride has been described as a water-soluble semi-synthetic derivate of camptothecin, a cytotoxic alkaloid which functions as a specific inhibitor of topoisomerase I. Topoisomerase I is known as an enzyme intimately involved in DNA replication as it relieves the torsional strain introduced ahead of the moving replication fork. Topotecan builds a “cleavable complex” with Topoisomerase I and DNA and the drug-enzyme-DNA complex ultimately causes double-stranded DNA breaks and the DNA double-strand breaks have been reported to lead to cell death, predominantly in replicating cells such as tumour cells. Replication-independent mechanism of cytotoxicity for topotecan have also been reported which may involve the induction of serine proteases and endonucleases because cytotoxicity also has been observed in cells not actively synthesising DNA. Overall topotecan has been reported to exhibit a broad spectrum of activity in xenograft tumour models which is comparable to that of other antineoplastic agents, and that has been confirmed in various more recently conducted studies. Topotecan in combination with cisplatin has been reported to show therapeutic synergism.

Pharmacokinetics
There were no pharmacokinetic study reports submitted as part of the application. A review of the literature was submitted which described the pharmacokinetic aspects of topotecan. The pharmacokinetics of topotecan has been investigated in three animal species (mice, rats, dogs) in non-clinical studies and in nonhuman primates. The studies were performed in normal and tumour-bearing animals.

Toxicology
A review of the literature was submitted which described the toxicology aspects of topotecan. There was no toxicology study reports submitted as part of the application. From the literature review, the toxicity of topotecan was described as similar across species and consistent with inhibition of topoisomerase I. Drug-induced lesions were identified in tissues with high cell turnover rates. The toxicity profile was characterised mainly by myelotoxicity (neutropenia, thrombocytopenia, lymphopenia and/or anaemia), lymphoid depletion in thymus and lymph nodes, and gastrointestinal effects (emesis, diarrhoea and intestinal crypt epithelial necrosis). Bone marrow haematopoietic cells, primarily neutrophils, demonstrated the highest sensitivity to topotecan. Minor lesions were noted in testes, hair follicles and ovaries, also tissues with rapid cellular turnover. Toxicities were not progressive and were reversible. Topotecan caused maternal and embryofetal toxicity in rats and rabbits with malformations in rats. No drug-related effects on mating, fertility or gonadal function were observed in males given topotecan at doses up to 0.68 mg/m^2. Superovulation was described in rats. Topotecan was described as genotoxic to mammalian cells.

Non-clinical studies using oral administration of topotecan were reported. Gastric mucosal hypertrophy/hyperplasia was noted in rats given topotecan orally in combination with GF120918A, a P-glycoprotein inhibitor. Systemic exposure of topotecan was reported to be significantly increased.

Environmental risk assessment exemption

The applicant has applied for an exemption of the Environmental risk Assessment based on the fact that products containing topotecan hydrochloride as active substance have been authorised in the EU for more than 10 years and that the 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.

Discussion on the Non-Clinical aspects
The non-clinical overview presented by the applicant provided an adequate overview of the pharmacological, pharmacokinetic and toxicological aspects of topotecan. There were no major issues or concerns raised for the approval of Topotecan Teva 1 mg/ ml, concentrate for solution for infusion (1 mg/ vial and 4 mg/ vial) from a non-clinical point of view.

The pharmacokinetics of topotecan seems generally well characterised. The pharmacokinetic profile of topotecan was investigated in mice, rats, dogs and nonhuman primate. There have been no new findings in the pharmacokinetic of topotecan which require amendments to the safety and efficacy evaluation or changes in SPC and PL.

The toxicity of topotecan was described as similar across species and consistent with inhibition of topoisomerase I.
Topotecan was described as genotoxic to mammalian cells. Long-term carcinogenicity studies with topotecan were not submitted. According to CPMP/SWP/997/96, “Note for Guidance on the pre-clinical evaluation of anticancer medicinal products” this is acceptable, because carcinogenicity studies are not usually required due to the intended therapeutic indications. However, topotecan is known to be genotoxic to mammalian cells and is probable carcinogen.

Topotecan distributes to the uveal tract/retina and skin. There were no specific phototoxicity studies that were conducted but it is stated that no toxicity was identified in the eye or skin of pigmented dogs and no reports of phototoxicity from the use in the clinic are available.

An exemption of the Environmental Risk Assessment can be accepted for this product on the basis that this is a generic application and no changes in the environmental risks, beside those which are already known for topotecan, are anticipated.

2.4 Clinical Aspects

Introduction
In the Clinical Overview, the applicant has provided a review of the literature with 28 publications dated from 1993 to 2008.

There were no detailed study reports from clinical trials submitted by the applicant. The application was submitted in accordance with Article 10(3) of Directive 2001/83/EC, where the applicant was not required to provide the results of pre-clinical tests and of clinical trials as the medicinal product is a generic of a reference medicinal product which is authorised for 6/10 years in a MS or in the Community.

Bio-equivalence exemption
According to section 5.1.6 of the guideline “Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98”, for parenteral solutions 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. Thus, as Topotecan Teva is to be administered as an aqueous intravenous solution containing topotecan in the same concentration as the currently authorised product, the applicant was not required to submit a bioequivalence study.

Clinical studies

The application contains adequate clinical data from the review of the publication literature for the proposed indication:

Topotecan monotherapy is indicated 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 (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).

The recommended dosage and method of administration of the generic product Topotecan 1 mg/ml is the same as that recommended for the reference product Hycamtin 1 mg/ml.

The recommended initial IV dosage of topotecan for the treatment of ovarian and small cell lung carcinoma in adults is 1.5 mg/m^2 body surface area/day administered by intravenous infusion over 30 minutes daily, for 5 consecutive days with a 3 week interval between the start of each course. Although the optimum duration of therapy remains to be established, it currently is recommended that topotecan therapy should be continued until a maximal response is achieved or dose-limiting toxicity develops.

In patients with cervical carcinoma the recommended dose of topotecan is 0.75 mg/m^2/day administered as 30 minute intravenous infusion daily on days 1, 2 and 3. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m^2/day and following the topotecan dose. This treatment schedule is repeated every 21 days for 6 courses or until progressive disease.

Pharmacodynamics
A review of the literature was submitted which described the clinical pharmacodynamic aspects of topotecan.
There were no clinical pharmacodynamic study reports submitted as part of the application.

Pharmacokinetics

A review of the literature was submitted which described the pharmacokinetic aspects of topotecan.
There were no clinical pharmacokinetic study reports submitted as part of the application.

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). 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 for 5 days, at doses of 0,5 to 1,5 mg/m^2, as a 30-minute infusion, 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.

Clinical efficacy and safety

The applicant has provided a review of 28 publications dated from 1993 to 2008 concerning the clinical use of topotecan for the proposed indications. There were no clinical or safety studies submitted as part of the application.

The efficacy and safety assessment of topotecan in patients with advanced ovarian carcinoma was based on the review of three non-comparative and two comparative published studies. All these studies were stated as conducted in accordance with Good Clinical Practice regulations. In these studies topotecan was administered intravenously, as a 30-minute infusion of 1,5 mg/m^2/day, for five consecutive days, every 3 weeks, but this could be increased or decreased according to the toxicity in the range from 1,0 to 2,0 mg/m^2/day.

Toxicity was generally managed by treatment delays and dose reductions and, when appropriate, the administration of G-CSF and/or GM-CSF. The main toxicity was haematological, which was predictable, of short duration, and non-cumulative. Topotecan has been shown to be efficient with an acceptable toxicity profile for the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent therapy.

Also, topotecan is used as second-line therapy for treatment patients with ovarian and small cell lung cancer (SCLC) who have relapsed after first-line chemotherapy. For the indication in patients with recurrent SCLC, efficacy and safety assessment of topotecan was based on he review of five publications on clinical trials in patients with SCLC, including one controlled, multicenter, randomized, phase III trial and 4 uncontrolled phase II studies. In the 4 uncontrolled phase II studies, in patients with recurrent or progressive SCLC, topotecan showed objective response rates ranging from 11 – 31 % in patients with sensitive disease and from 2 – 7 % in patients with refractory disease. In the large randomized, controlled trial, topotecan used as a single agent was at least as efficient as the combination chemotherapy regimen CAV in the treatment of patients with recurrent SCLC.

Improvements in quality-of-life in patients with recurrent small-cell lung cancer, which resulted in improved palliation of several symptoms, including dyspnoea, anorexia, fatigue, hoarseness and interference with daily activities have been described.

The efficacy and safety of topotecan in combination with cisplatin in patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IV B disease was based on the review of a published study. This study evaluated the combination regimen topotecan/cisplatin (CT) with that of single agent cisplatin (CPT) in a large clinical trial, performed in women with histologically confirmed, stage IV B recurrent or persistent carcinoma of the cervix for whom curative treatment with surgery and/or radiotherapy was not an option. The main toxicity observed was myelosuppression, which was greater in the CT arm although bone marrow toxicity did not appear to be cumulative and was generally manageable.

The generic product has the same amount of the active substance as the reference product. Topotecan Teva 1 mg/ml, concentrate for solution for infusion is a ready-to-use solution for infusion for

intravenous administration which is already reconstituted whereas the reference product is a powder for concentrate for solution for infusion. Therefore, the pharmaceutical form is different between the reference product and the generic product.

Additional data
No additional data was submitted from the applicant

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

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule for Topotecan Teva should follow the PSUR submission schedule for the reference medicinal product, Hycamtin.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system, version 6 dated November 2008, 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. The company must ensure that this system is in place and functioning before the product is placed on the market.

- **Risk Management Plan**

No description of Risk Management plan (RMP) has been provided by the applicant. The applicant stated that the generic product refers to a well known active substance which has been marketed for many years throughout the EU. The applicant considers no need for additional risk minimisation measures apart from routine pharmacovigilance.

- **User consultation**

The user testing of the package leaflet was performed. The criterion for a successful Readability Test was fulfilled. The user testing of the package leaflet was judged acceptable.

Discussion on Clinical aspects

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

The clinical overview provides an adequate overview of the clinical pharmacology, efficacy and safety of topotecan. There were no clinical study reports submitted as part of this application. A bioequivalence study was not required since the generic product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the reference product. All the published studies that supported the ovarian cancer indication were stated as conducted in accordance with Good Clinical Practice regulations and provided reliable data on anti-tumour activity of topotecan in the treatment of advanced ovarian carcinoma. When used in combination with cisplatin, the full prescribing information for cisplatin should be consulted. Prior to administration of the first course of topotecan, patients must have a baseline neutrophil count of $\geq$ 1.5 X 10^9/l, and a platelet count of $\geq$ 100 x 10^9/l.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The dossier in question refers to a generic product with a well known active substance which has been marketed for many years throughout the EU. The applicant considers no need for additional risk minimisation measures apart from routine pharmacovigilance. The Rapporteur endorses this position.

The generic product has the same amount of the active substance as the reference product. Topotecan Teva 1 mg/ml, concentrate for solution for infusion is a ready-to-use solution for infusion for intravenous administration which is already reconstituted compared to the reference product, which is a powder for concentrate for solution for infusion. Therefore, there is a difference between the reference product and the generic product, which is a change in the pharmaceutical form. However, the concentrate for solution for infusion of the generic product is exactly the same concentration as the reference product after reconstitution and the proposed dosage regimens are identical to those currently registered for the reference product. As the intravenously administered solution for infusion is given in the same concentration as the reference product, this pharmaceutical form is considered appropriate.

The qualitative and quantitative composition of Topotecan Teva 1 mg/ml, concentrate for solution for infusion shows a difference is the content of mannitol as compared to the reconstituted solution of Hycamtin (topotecan powder for concentrate for solution for infusion). The concentrate for solution for infusion contains no mannitol whereas the powder for concentrate for solution for infusion does contain mannitol. Comparative studies on the formulation and impurity profile of Topotecan Teva 1mg/ml concentrate for solution for infusion with those of the reference product show that they are essentially similar. Therefore, the safety and efficacy characteristics of the generic product are comparable with the originator product. Topotecan Teva 1 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.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Quality
The quality of Topotecan Teva has been satisfactorily described. Satisfactory pharmaceutical documentation has been submitted for marketing authorization in line with EU and ICH requirements.

The synthesis of the active substance topotecan hydrochloride is adequately described and impurities are characterised, in line with current ICH guidelines. The manufacturing process of the medicinal product Topotecan Teva is robust and ensures batch consistency. Analytical methods have been validated. The stability data on the active substance support the proposed re-test period, and the stability data on the finished product support the shelf life as stated in the SPC.

In conclusion, information on development, manufacture and control of the active substance and medicinal product have 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.

At the time of the Opinion no quality issues remained unresolved.

Overall conclusion and Benefit/risk assessment

The non-clinical and clinical literature review provides a consistent overview of the pharmacological, pharmacokinetic and toxicological aspects of topotecan. Therefore, there were no objections to the approval of Topotecan Teva 1 mg/ml concentrate for solution for infusion (1 mg/1 ml and 4 mg/4 ml) from a non-clinical and clinical point of view. The use of topotecan should be confined to units specialised in the administration of cytotoxic chemotherapy and should only be administered under the supervision of a physician experienced in the use of chemotherapy.

An exemption for the ERA can be given for this product since this generic application has identical posology to the active substance. The CHMP agrees that no changes in the environmental risks that are not already known for topotecan are to be anticipated.

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.

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

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

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Topotecan Teva in the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy and 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) was favourable and therefore recommended the granting of the marketing authorisation.