EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Potactasol

International nonproprietary name: topotecan

Procedure No. EMEA/H/C/2282

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 Actavis Group PTC ehf submitted on 12 July 2010 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Potactasol 1 mg and 4 mg (1 mg/ml) powder for concentrate for solution for infusion, 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'.
This application has been submitted as a duplicate to the marketing authorization for Topotecan Actavis 1 mg and 4 mg (1 mg/ml) Powder for concentrate for solution for infusion - EU/1/09/536/001, 002), in accordance with Artic1e 82(1) of Regulation (EC) 726/2004.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Community on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC, as amended.

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, 1 mg and 4 mg, powder for concentrate for solution for infusion**
- Marketing authorisation holder: **SmithKline Beecham plc.**
- Date of authorisation: (dd-mm-yyyy) **12-11-1996**
- Marketing authorisation granted by: **Community**
- Community Marketing authorisation number(s):
  **1 mg: EU/1/96/027/004 (5 vials), EU/1/96/027/005 (1 vial)**
  **4 mg: EU/1/96/027/001 (5 vials), EU/1/96/027/003 (1 vial)**

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

- Not applicable

The Rapporteur appointed by the CHMP was Dr. Laslop.

## Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

## Licensing status:

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

## *1.2. Steps taken for the assessment of the product*

- The application was received by the EMEA on 12 July 2010.
- The procedure started on 18 August 2010.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 24 September 2010 (Annex 1). A revised Assessment Report following receipt of CHMP comments was circulated on 15 October 2010 (Annex 2).
- During the meeting on 18 – 21 October 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Potactasol on 21 October 2010.

# 2. Scientific discussion

## *2.1. Introduction*

Potactasol 1 mg and 4 mg (1 mg/ml) powder for concentrate for solution for infusion is a generic medicinal product containing topotecan hydrochloride as active substance. The reference medicinal product Hycamtin 1 mg and 4 mg powder for concentrate for solution for infusion has been centrally authorised on 12 November 1996. The active substance of the reference product is topotecan also present as topotecan hydrochloride salt.

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

Potactasol is indicated (as monotherapy) for treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy and 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 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 Applicant for the duplicate marketing authorization is the same that applied for the original marketing authorization (Topotecan Actavis 1 mg and 4 mg (1 mg/ml) Powder for concentrate for solution for infusion - EU/1/09/536/001, 002). The European Commission granted a marketing authorisation valid throughout the EU for “Topotecan Actavis 1 mg and 4 mg (1 mg/ml) Powder for concentrate for solution for infusion” to Actavis Group PTC ehf. on 24 July 2009.

Compared with the original marketing authorization the applicant has applied for the following additional indication:

*Topotecan monotherapy is indicated for the treatment of:*
- *patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.*

## *2.2. Quality aspects*

### 2.2.1. Introduction

The medicinal product Potactasol contains the active substance topotecan hydrochloride as sterile lyophilised powder for concentrate for solution for infusion. Two strengths 1 mg/vial and 4 mg/vial have been developed. The vials contain 1 mg topotecan (as hydrochloride), with a 10 % overage of fill or 4 mg topotecan (as hydrochloride), respectively. Other ingredients are mannitol (bulking agent), tartaric acid (stabilizer) and sodium hydroxide and hydrochloric acid (pH adjustment).

The medicinal product is packed into type I colourless borosilicate glass vials (5 ml or 8 ml), with a grey bromobutylic stopper and an aluminium flip-off cap with a white or blue polypropylene disk, respectively. Each vial is packaged in an individual carton box.

## 2.2.2. Active Substance

The chemical name of the active substance topotecan hydrochloride is: (S)-10-[(Dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1Hpyrano[3',4':6,7]indolizino-[1,2-b]quinoline-3,14(4H,12H)-dione monohydrochloride. The International Non Property Name (INN) is topotecan.
Topotecan hydrochloride is a yellow to orange powder. Topotecan hydrochloride has one chiral center and is optically active.
At room temperature, topotecan hydrochloride is freely soluble in water, slightly insoluble in methanol and ethanol and insoluble in acetone and acetonitrile, n-hexane, tetrahydrofuran and ethylacetate. Topotecan hydrochloride is considered hygroscopic. There is no Ph. Eur. monograph for topotecan hydrochloride.

The active substance has been fully characterised and the chemical structure of topotecan hydrochloride has been elucidated through elemental analysis, ultraviolet (UV), infrared (IR), mass spectrometry (MS) and nuclear magnetic resonance spectroscopy (NMR). All data are consistent with the proposed structure.

***Manufacture***

Topotecan hydrochloride is a semi-synthetic, water soluble analogue of camptothecin. It is synthesized by a two-step reaction followed by re-crystallisation and purification. Detailed information about the manufacturing, process validation and control of critical manufacturing steps has been supplied in the form of an active substance master file (ASMF). At the time of the opinion, only one active substance manufacturer is authorised.
All manufacturing steps are adequately described. Adequate in process controls are in place and appropriate specifications have been adopted for the starting materials, solvents, reagents and auxiliary materials. All relevant impurities, degradation products and residual solvents have been appropriately characterized.

***Specification***

As no monograph of topotecan hydrochloride exists in the Ph. Eur. or USP, in-house specifications have been set for the active substance, in accordance with the principles of ICH guidelines.
The active substance specifications are considered appropriate and include tests for appearance, identification (HPLC and FT-IR spectra), assay and purity (HPLC), specific rotation, residual solvents (GC), heavy metals, water content (Karl-Fischer determination), chloride content (titration), residue on ignition and bacterial endotoxins. The analytical procedures have been satisfactorily described and validated in accordance with the ICH guidelines.
The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data have been presented and all batches were in compliance with the predefined active substance specification.

***Stability***

The manufacturer has conducted stability studies at long- term (5ºC) and accelerated (25ºC/ 60%RH) conditions on two batches. Additionally, forced degradation studies and stress studies have been performed. The specifications include tests for appearance, assay and purity by HPLC and water content by Karl Fischer. The test methods for stability are the same as those used in the active substance specifications above.
From thermal stability studies could be concluded that topotecan hydrochloride is sensitive to exposure of light, moisture and excessive heat. A justified retest period has been defined and agreed. The stability studies are performed in accordance with the ICH guidelines and EMEA Guidance on Stability Testing.

Topotecan hydrochloride is double packed in low density polyethylene (LDPE) bags. The package bags are sealed with twist before inserted into aluminium foil bags that no not contact with the product. The container-closure system of topotecan hydrochloride is in accordance with the EMEA guideline CPMP/QWP/4359/03.

## 2.2.3. Medicinal Product

***Pharmaceutical Development***

The medicinal product Potactasol 1 mg and 4 mg powder for concentrate for solution for infusion is a generic of the reference medicinal product Hycamtin, approved centrally on 12th November 1996.

Potactasol (1 mg and 4 mg) powder for concentrate for solution for infusion has the same qualitative and quantitative composition as Hycamtin in terms of active substance. In terms of excipients, the qualitative and quantitative composition of Potactasol 4 mg is identical to Hycamtin. Potactasol 1 mg, on the contrary, contains twice as much mannitol compared to Hycamtin 1 mg powder for concentrate for solution for infusion. Other excipients in the 1 mg strength are identical to the reference medicinal product.

The Marketing Authorisation Holder focused the product development on the optimization of the manufacturing procedure and the confirmation of the medicinal product stability. Furthermore, the compatibility with the reconstitution solvent (water for injections) and stability of the medicinal product after reconstitution and dilution have been studied.

Potactasol is administrated intravenously and is therefore classified as 100% bioavailable. Therefore, no bioequivalence study versus the reference medicinal product was performed.

***Adventitious agents***

No component of human or animal origin is used for the finished product manufacture, therefore there is no BSE/TSE risk. BSE/TSE declarations from the manufacturers of the excipients are provided.

***Manufacture of the Product***

The manufacturing process of Potactasol involves: sterilization of the container closure system, preparation of the topotecan solution, sterilization by filtration, freeze-drying, vials capping, and external vial washing and drying. The manufacturing method is essentially the same for the two strengths. The manufacturing process is satisfactorily described and validated, and adequate in-process controls are applied.
All critical process parameters have been identified and controlled by appropriate in-process controls. The manufacturing process demonstrates to be reproducible and provides a finished product that complies with the in-process and finished product specifications.

***Product Specification***

The medicinal product specifications for Potactasol at batch release include tests for appearance, identification (HPLC, UV), water content (Karl Fischer), dissolution time (in water for injections), uniformity of content, assay and impurity content (HPLC), sterility and bacterial endotoxins. The specifications for the reconstituted solution in water for injections include tests for appearance, colour, clarity, visible and sub-visible particles and pH.

All tests included in the specification have been satisfactorily described and validated, according to the state of the art. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Batch analysis results comply with the

proposed specification and confirm consistency & uniformity of manufacture and indicate that the process is under control.

***Stability of the Product***

Stability studies have been performed on 6 production scale batches under long term conditions (25°C ± 2°C/60% RH ± 5°C), accelerated conditions (40°C ± 2°C/75% RH ± 5°C) and intermediate conditions (30°C ± 2°C/65% RH ± 5% RH). In addition, photo-stability studies have been performed, as well as stability studies after reconstitution with water for injections and stability studies after dilution in solution for infusion (0.9% NaCl and 5% glucose).

The shelf-life specifications include the same parameters and tests as the release specifications. In all cases the stability results presented were satisfactory and support the shelf life and storage conditions as defined in the SPC.

## 2.2.4. Discussion on chemical, and pharmaceutical aspects

The quality of Potactasol is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. There are no major deviations from 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 Potactasol is under control and ensures both batch to batch reproducibility and compliance with standard procedures and specifications. The analytical methods have been validated and ensure consistent quality of the active substance and the finished product. The stability data on the active substance support the proposed re-testing period, and the stability data on the finished product support the shelf life as stated in the SPC.

In comparison with the EU reference product, Potactasol contains the same qualitative composition in terms of active substance and excipients. Both the EU reference product and Potactasol exhibit similar dissolution profiles.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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.

## *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 88 publications from 1983 to 2007. The applicant submitted a justification why no additional studies are required.

## Pharmacology

A review of the literature was submitted which described the pharmacologic aspects of topotecan. Accordingly, topotecan hydrochloride has been reported as a water-soluble semi-synthetic derivate of camptothecin, a cytotoxic alkaloid and to be a specific inhibitor of topoisomerase I. Topotecan builds a "cleavable complex" with Topoisomerase I and DNA. The drug-enzyme-DNA complex ultimately causes double-stranded DNA breaks when DNA replication occurs and leads to cell death predominantly in replicating cells such as tumour cells. Topotecan is an S-phase-specific drug, but replication-independent mechanism of cytotoxicity 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 evaluated in three animal species (rats, mice and dogs), used in the preclinical programme and in nonhuman primate. 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 were no toxicology studies submitted as part of the application.
The toxicity of topotecan was 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.
The genotoxic potential of topotecan was investigated *in vitro* using bacterial tests and mammalian cells assay and *in vivo* with mouse micronucleus tests. As would be expected from its pharmacological activity, topotecan was genotoxic to mammalian cells.
The reproductive toxicity of topotecan was investigated in rats and dogs. Topotecan was evaluated for maternal toxicity as well as embryotoxic, fetotoxic and teratogenic potential in female rabbits and rats.

There are no published preclinical studies available in the scientific literature regarding the local tolerance of topotecan.

## Ecotoxicity/Environmental risk assessment

An Environmental Risk Assessment was not submitted with this marketing authorization application.

The applicant has applied for an exemption of the Environmental risk Assessment based on the fact that products containing topotecan hydrochloride as drug 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 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 raised during the assessment from a non-clinical point of view.

The pharmacology of topotecan has been widely investigated, as reflected in the review submitted by the applicant.

The pharmacokinetics of topotecan seem generally well characterised. The pharmacokinetic profile of topotecan was investigated in mice, rats, dogs and nonhuman primate.

There have been no new findings which require amendments of 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. No specific phototoxicity studies have been conducted but it is stated that no toxicity was identified in the eye or skin of pigmented dogs and no reports of phototoxicity from 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.

### 3.4 Clinical Aspects

#### Introduction

The applicant has provided an updated review of the clinical use of topotecan for the proposed indications with 78 publications from 1989 to 2007.

There were no detailed study reports from clinical trials submitted by the applicant. The application was submitted in accordance with Article 10(1) 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 Potactasol 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.*

- *Topotecan monotherapy is indicated for the treatment of patients with relapsed small cell lung Cancer [SCLC] for whom re-treatment with the first-line regimen is not considered appropriate (see section 5.1).*

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

**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.

**Pharmacokinetic**

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.

Absorption

Following intravenous administration of topotecan in adults with solid tumors, 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.

Distribution

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.

Elimination

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 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 78 publications dated from 1989 to 2007 concerning the clinical use of topotecan for the proposed indications. There were no clinical or safety studies submitted as part of the application.

Topotecan as monotherapy for the treatment of metastatic ovarian carcinoma after failure of first-line or subsequent therapy, was studies in 5 clinical trials, including 3 uncontrolled phase II studies and 2 controlled phase III trials. In 3 uncontrolled phase II studies, in patients with platinum-resistant/refractory epithelial ovarian cancer, topotecan showed objective response rates ranging between 14 – 17 % with a median survival in range 8,7 – 11 months.

Topotecan as second-line therapy for treatment patients with small cell lung cancer (SCLC) who have failed or relapsed after first-line chemotherapy was studied in five clinical trials, including one controlled, multicenter, randomized, phase III trial and 4 uncontrolled, phase II studies. In 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 a large randomized controlled trial topotecan used as a single agent was at least as efficient as combination chemotherapy regimen CAV in the treatment of patients with recurrent SCLC. The recommended initial IV dosage of topotecan for the treatment of 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.

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.

In addition, in combination with cisplatin, topotecan is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IV B disease. Safety of combination regimen topotecan/cisplatin (CT) was compared 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 were included in the study. Regarding safety of topotecan, in this trial was demonstrated that, although myelosuppression was greater in the CT arm, bone marrow toxicity did not appear to be cumulative and was generally manageable."

Following the CHMP adoption on 23 September 2010 of variation II/59 for Hycamtin, the reference medicinal product, sections 4.2, 4.4 and 4.8 of the Potactasol Summary of Product Characteristics have been updated regarding severe bleeding, pancytopenia, potential fatal outcome of sepsis and interstitial lung disease and dehydration as a consequence of severe diarrhoea. The Package Leaflet has also been updated accordingly.

## Additional data

No additional studies were submitted as part of this application.

## Post marketing experience

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

## 3.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule for Potactasol 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 5.03 of 12 October 2009, 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 and whilst the product is placed on the market

- **Risk Management Plan**

The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified.

Routine pharmacovigilance activities according to volume 9A/ICH will be undertaken whilst the product is in the market, including careful review of individual case safety reports, literature review, signal detection procedures and generation of the required safety reports. Specific risk minimisation activities are not envisaged as the safety aspects of the product are well characterised and therefore a Risk Minimisation plan is not required.

- **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 Potactasol and no additional clinical studies are needed.
A bioequivalence study is not required since the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised product. The recommended dosage and method of administration of the generic product Topotecan 1 mg/ml is the same as that recommended for the product Hycamtin 1 mg/ml. 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.

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.

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.

## 3.6 Overall conclusions, benefit/risk assessment and recommendation

### 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 are no objections to approval of Potactasol 1 mg/ ml- powder for concentrate for solution for infusion (1 mg/ vial and 4 mg/ vial) from a non-clinical and clinical point of view.

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.

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

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

**Recommendation**

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Potactasol in 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 thefirst-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.

was favourable and therefore recommended the granting of the marketing authorisation.