SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Hycamtin. This scientific discussion has been updated until 1 September 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Ovarian cancer is the fourth most common cause of cancer death in women. At time of diagnosis, the cancer has spread outside the pelvis in at least 60% of the patients. At the time of the evaluation, overall five-year survival was about 20%. The treatment of advanced ovarian carcinoma generally consisted of surgery followed by chemotherapy. Commonly used chemotherapy regimens have been platinum-based and cyclophosamide/cisplatin was a widely used combination regimen at the time of the evaluation. Paclitaxel in combination with cisplatin had shown promising results as first-line therapy. Although the response rate to first-line chemotherapy is relatively high, the disease will relapse in the majority of patients. Ovarian carcinoma, which fails first-line therapy, is not curable.

Topotecan is a semisynthetic structure analogue of the natural alkaloid camptothecin. It is water soluble with an intact lactone ring. The lactone ring may open in a reversible pH-dependent reaction, forming a carboxylate derivative. Only the lactone form is pharmacologically active, inhibiting topoisomerase 1. This nuclear enzyme is crucial for DNA replication, i.e. proliferation, DNA repair and transcription. Topoisomerase 1 inhibitors bind only to the DNA-enzyme complex. This binding is rapidly reversible, allowing religation within 30 min. after drug removal. Following prolonged drug exposure, DNA fragmentation occurs leading to apoptotic cell death.

The proposed indication is treatment of metastatic carcinoma of the ovary after failure of first-line or subsequent therapy. The proposed dosage is 1.5 mg/m^2/day administered intravenously during 30 min. for 5 consecutive days every 3 weeks.

2. Chemical, pharmaceutical and biological aspects

Hycamtin is presented as powder for solution for infusion. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan. The product should be reconstituted with 4 ml of water for injection and diluted with 0.9% sodium chloride or 5% glucose intravenous infusion. It contains mannitol as bulking agent, tartaric acid as a stabiliser as well as hydrochloric acid and sodium hydroxide to adjust the pH to 2.5-3.5. Hycamtin is packaged in 5 ml vials of Type I flint glass (Ph. Eur.) with grey siliconised butyl rubber stoppers with aluminium flip-off seals.
Topotecan hydrochloride is hygroscopic with a low solubility in organic solvents except methanol. Its aqueous solubility decreases with increasing pH. In aqueous solution it can undergo pH-dependent reversible opening of the lactone ring (below pH 4 no open form is present, above pH 9 more than 95% is hydrolysed). Topotecan is light and heat sensitive. The purpose of the pharmaceutical development was to produce a product stable enough for intravenous injection. The lyophilised form was chosen due to the stability problems arising from the above-mentioned properties of the drug substance.

Topotecan is semisynthetically manufactured from the plant-derived alkaloid camptothecin. The starting material may be obtained from two natural sources - Chinese (Acuminata) and Indian (Mappia). Purification of the crude extract from either source is required. The main steps in the synthesis involve reduction and selective oxidation of the quinoline moiety of camptothecin, followed by the introduction of an *N,N*-dimethylaminomethyl side-chain. The structure of topotecan is proved by elementary analysis, interpreted ultra violet-, infrared-, nuclear magnetic resonance-, and mass-spectrometry spectra. Serial batch analyses confirmed the consistency of the manufacturing process, using tests which were sufficiently validated.

Topotecan is chiral and contains one stereogenic (asymmetric) centre with the *S* configuration. The molecule is homochiral to camptothecin, for which the stereochemical purity is ascertained by chiral chromatography. The antipode has not been found in any batch and there is no known mechanism to

racemise camptothecin under the conditions applied during the synthesis of topotecan. Thus, the stereochemical purity is considered to be under control.

Five impurities have been qualified at their specification levels. Owing to the limited number of batches manufactured, the limits for impurities should be reassessed when more experience is gained. Also with respect to the finished product, limits for impurities and degradation products will be reassessed when more experience is gained.

With respect to other ingredients, mannitol, tartaric acid, hydrochloric acid, sodium hydroxide and water for injection were claimed to follow the requirements of the Ph. Eur. To show conformance with the Ph. Eur., certificates of analyses should be submitted when available. Limits for microbial purity of water for injection were confirmed not to exceed 10 CFU/100 ml and of topotecan hydrochloride, mannitol and tartaric acid not to exceed 10^2 CFU/g.

The finished product is manufactured by aseptic processing. Due to equipment-related graphite contamination of the drug solution, a pre-filtration using 0.45µm filter is included before two consecutive sterile filtrations using 0.2µm filters to assure sterility. Thereafter, the solution is aseptically filled into vials before lyophilisation. The manufacturing process is satisfactory validated and relevant in-process controls are performed. Bioburen is included as a periodic in-process test.

Although topotecan degrades under stressed conditions, it appears to be stable in long-term stability studies. The proposed shelf life of 24 months below 30°C can be accepted. Chemical stability of reconstituted as well as diluted solution has been demonstrated, but from a microbiological point of view, immediate use is required. If reconstituted under strict aseptic conditions (e.g. in a LAF-bench), 12 h in room temperature or 24 hours at 2-8°C can be accepted from the first breaking of the vial until the infusion to the patient is completed. Due to its light sensitivity, it must be protected from light during long-term storage.

The initial shelf life at the time of the Marketing Authorisation was 24 months. The Marketing Authorisation Holder applied for an extension of the shelf life to 3 years through a Type I variation. The stability data provided demonstrated that the specifications are all met and that a shelf life of 3 years is acceptable.

Additional presentations of a 1 mg vial in packs of 3 and 5 vials were approved following a Type II variation. The formulation of the bulk solution is identical to the formulation for the already approved 4 mg vials. The difference between the 1 and 4 mg vials is the fill weight and vial size. The 1 mg lyophile will be reconstituted to the same concentration as the 4 mg lyophile i.e. 1 mg/ml. However, the 1 mg vial contains a 10 % filling overage to ensure that 1 mg can be withdrawn from each vial, in line with European Pharmacopoeial recommendations for extractable volumes.

3. Toxico-pharmacological aspects

Pharmacodynamics

The mechanism of action of topotecan has been delineated in tumour cell lines and cell free systems, and is, in comparison with many other anti-cancer drugs, well characterised. It includes the depicted interaction with the target enzyme topoisomerase 1 and the dependency of DNA replication for the cytotoxic effect. Topoisomerase 1 is involved in the cleavage and religation of the DNA ahead of the replication fork and is therefore crucial in DNA replication, DNA repair as well as transcription. Topotecan selectively inhibits the religation step, which stabilises the enzyme-cleaved DNA complex leading to the formation of 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 underlying the cytotoxic effects of topotecan. Cytotoxicity appears to be time and concentration dependent. IC_{50} values ranging from about 1-800 nM were obtained with various cell lines *in vitro*. However, no '*in vivo* mechanistic studies', e.g. relationships between drug exposure and single strand breaks, cytotoxicity or reversibility, were carried out. Studies designed to elucidate schedule dependent activity indicated that prolonged exposure is associated with increased cytotoxic effect. Thus, the proposed schedule for licensing, a 30-min infusion each day for 5 days is, at least partly, supported by preclinical data.

Cell lines with low topoisomerase 1 level or with altered or reduced binding of topotecan to topoisomerase 1 was shown to be resistant to its cytotoxic activity. Topotecan also seems to be a substrate, albeit rather poor, for the multidrug resistance associated P-glycoprotein "drug extrusion pump". In general, cisplatin resistant sublines were not resistant to the activity of topotecan. However, the level of *in vitro* cross-resistance with topotecan in tumour samples from patients with clinical, cisplatin- or paclitaxel-resistant disease was not investigated.

It is generally accepted that activity against specific cell lines *in vitro* and *in vivo* poorly predicts activity against corresponding tumour types in patients. *In vitro* systems, using fresh tumour samples and various techniques and endpoints, may confer a good correlation with clinical activity, both with respect to diagnostic groups and in individual patients. An attempt in this direction was included in the present documentation. However, the predictive value of the technique chosen, the clonogenic assay, is questionable.

Overall, submitted pharmacological studies provide no obvious rationale for exploring the activity of topotecan in patients with ovarian carcinoma failing platinum and/or paclitaxel based therapy.

General pharmacodynamics: In rats, renal function was significantly affected at 15-mg/m^2 topotecan, a dose producing only mild general toxicity. In contrast, no effects were seen on the central nervous system activity in mice, on the cardiovascular or respiratory systems in rat and dog or on the gastrointestinal system in mice. However, the doses used were considerably lower than those inducing general toxicity in the same species.

Product interactions: *In vitro* and *in vivo* studies indicated a possible synergistic effect between topotecan+cisplatin. Studies in mice tumour models confirmed that the antitumour activity of etoposide was antagonised by concurrent administration of topotecan. However, a synergistic effect was observed when the drugs were given on sequential days. Studies of potential pharmacodynamic or pharmacokinetic interactions are limited. One study showed no effect of topotecan on the activities of the rat cytochrome P450 enzymes CYP1A, CYP2B, CYP2E, CYP3A and CYP4A.

Pharmacokinetics

The pharmacokinetic profile of topotecan was studied in the mouse, rat and dog, the species used in the preclinical programme. In tumour-bearing mice given a single intravenous injection of [^{14}C] topotecan, radioactivity was rapidly distributed into all tissues, including tumours. Topotecan is metabolized to a minor extent mainly by N-desmethylation. The N-desmethyl derivatives of topotecan and the inactive carboxylate form accounted for 4% and 17% of the dose in the excreta of the rat and the dog, respectively.

Toxicology

Single dose toxicity was investigated in rodents and dogs following intravenous administration of topotecan. Doses of 56, 148 or 74 mg/m^2 were lethal in mice, rats or dogs respectively. Target organs of toxicity were bone marrow, lymphoid tissues, gastrointestinal tract and ovaries.

Repeat dose toxicity following intravenous administration of topotecan was studied in mice (5 days study), as well as in rats and dogs (5-28 days studies). In addition, rats were administered topotecan by the oral route during 6 months. All species showed signs of toxicity consistent with the pharmacological effects of topotecan. At or below the maximum tolerated dose (MTD, being 4.7 mg/m^2/day in rats and 1.3 mg/m^2/day in dogs), the toxicity profile was characterised by myelotoxicity (neutropenia, thrombocytopenia, lymphopenia and anemia), lymphoid depletion and gastrointestinal effects. Furthermore, other tissues with a rapid cell turnover, such as hair follicles and testis were affected. The main dose-limiting toxicity was the effect on bone marrow. In surviving animals, effects were reversible after termination of treatment. The available animal data do not indicate a potential for toxicity in major organs other than expected.

Reproductive toxicity Topotecan caused malformations and embryo-foetal toxicity at doses that are less than those recommended clinically. Such effects are characteristic of many neoplastic agents. Thus, topotecan is contraindicated in pregnant women.

Genotoxicity and carcinogenicity Topotecan was not genotoxic in bacterial tests. However, as predicted based on its pharmacologic activity, genotoxic effects were evident in mammalian cells (mouse lymphoma assay, human lymphocyte assay, micronucleus test in mice). Topotecan is likely to

be carcinogenic. No carcinogenicity studies were performed which is acceptable regarding the intended use of topotecan.

Environmental risk assessment Topotecan that enters the environment is expected to distribute to the aquatic compartment and undergo rapid photolysis. Thus, no significant environmental risks or ecotoxicity are expected.

4. Clinical aspects

The core clinical documentation of topotecan consists of 4 phase II/III studies in patients with advanced ovarian carcinoma. In addition, 13 phases I studies in female and male patients have been conducted.

Pharmacodynamics

The phase I programme consisted of 13 studies with conventional aims and designs, of which 12 were performed in patients with advanced solid tumours and one in patients with leukemia. Altogether more than 370 patients were included. Five of the studies were conducted with the proposed schedule for licensing. In two of the studies, granulocyte-stimulating factor (G-CSF) was added.

The MTD was found to be 1.5 mg/m^2/day for 5 consecutive days every 3 weeks, but might be lower in patients extensively pretreated with chemotherapeutic agents or in patients with low performance status. Overall, the toxicity profile seemed to be essentially schedule independent although prolonged infusion may be associated with slightly more muco-cutaneous side effects. Neutropenia was dose limiting. The use of G-CSF was not conclusively demonstrated to alter MTD, and thrombocytopenia may in this situation become dose limiting.

Pharmacokinetics

The pharmacokinetic documentation of topotecan consists of 4 phase I studies in about 170 male and female cancer patients. The proposed dose regimen of licensing as well as single intravenous doses up to 22.5 mg/m^2 has been administered. The pharmacokinetics of topotecan in the target population was depicted by a population pharmacokinetic analysis. The non-linear mixed effects modelling (NONMEM) approach was used on data from 100 patients with ovarian carcinoma in study 039.

A high performance liquid chromatography (HPLC) method with fluorometric detection was used for the analyses of topotecan and its inactive carboxylate form in plasma. In the population analysis, a slightly modified method was used to measure 'total topotecan' (topotecan + carboxylate derivative) in plasma. Due to the instability of the lactone in plasma requiring careful handling and quick processing of the samples, a method measuring both the active and inactive form was considered more convenient for use in Phase III studies. Both methods were adequately described and validated. Only limited data on the excretion of topotecan in urine were available. Basic pharmacokinetic properties, such as clearance (Cl), volume of distribution (Vd) and protein binding have been determined for both the pharmacologically active lactone and total topotecan, which includes the inactive carboxylate form.

The plasma protein binding of topotecan was low (35%). The blood/plasma distribution ratio decreased from 1.2 to 0.8 during 4 hours incubation in whole blood, with the percentage bound to blood cells decreasing from 53% to 20%. Binding to human tissues has not been studied, but the relatively large Vd of topotecan indicated a high tissue uptake. For the active lactone, values for Vd at steady state (Vdss) were 132 liters (SD 57 liters). Data from a study comparing oral and intravenous administration showed an absolute bioavailability of about 30%.

Following an intravenous dose of 1.5 mg/m^2, the elimination half-life ($t_{1/2}$) was about 3 h [range 1.9-3.8h]. The plasma levels of topotecan declined biphasically. In the population analysis, $t_{1/2}$ of the first phase was 0.35 h and of the terminal phase 3.5 h. Approximately 80% of the area under plasma concentration-time curve (AUC) was associated with the terminal phase.

At physiological pH, topotecan is rapidly hydrolysed to the inactive carboxylate form. This is a reversible, pH-dependent reaction. The plasma clearance of topotecan is high (1000-1200 ml/min, up

to 2700 ml/min was reported) while clearance values of 'total topotecan' are lower (about 300 ml/min in the population pharmacokinetic analysis).

The elimination of topotecan has only been partly elucidated. With respect to excretion, data are very limited. No recovery study with radiolabelled topotecan has been conducted. In urine, about 20-60% of the dose was detected but due to inter-conversion occurring at urinary pH, only values of 'total topotecan' are available. Faecal excretion has not been studied. In bile from one patient, substantial concentrations of topotecan were found. Based on human *in vitro* data, metabolism seems to be a minor route of elimination.

No *in vivo* interaction studies have been conducted. *In vitro* studies with human liver microsomes showed no inhibition of the cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A4 or CYP4A or of the cytosolic dihydropyrimidine dehydrogenase or xanthine oxidase. In the population analysis, corticosteroides, granisetron, ondansetron or morphine did not appear to affect the pharmacokinetics of 'total topotecan'. Based on the available data, possible interaction with renally excreted drugs cannot be predicted.

Over a dose range of 0.5 to 22.5 mg/m^2/day, the maximum plasma concentration (C_{max}) and AUC from time 0 to infinity ($AUC_{0-\infty}$) increased approximately proportionally. Cl and Vdss were also similar over the studied dose range. The sparse data following repeated dosing showed no signs of time dependency of the pharmacokinetics of topotecan within a 5-day course.

Clearance of total topotecan was reduced by 30% in patients with elevated bilirubin levels in comparison to patients with normal hepatic function. However, as patient variability in clearance was large (CV about 60%) it is not possible to evaluate the clinical significane of this observation. Three patients with serum bilirubin between 1.7 and 10 mg/dl were able to tolerate 1.5 mg/m^2/day for 5 days every 3 weeks. However, these data are insufficient as a basis for dose recommendations for this patient group. Furthermore, there is no experience of topotecan use in patients with severe hepatic impairment due to cirrhosis.

In a limited number of patients, clearance of topotecan correlated with creatinine clearance (Cl_{CR}) but this was not confirmed for total topotecan in the population analysis. Based on data from a few patients, the recommended dose in patients with Cl_{CR} between 20-39 ml/min is 0.75 mg/m^2/d. There is no experience of topotecan use in patients with severe renal impairment.

Body surface area, renal function and performance status were identified as factors for prediction of exposure and toxicity in individual patients. A positive correlation between the exposure of both topotecan and 'total topotecan' and the percent decrease in white blood cells has been observed, but since the ratio of lactone/ring opened form (active/inactive drug) changes over time after the infusion, total topotecan is only accepted as an incomplete surrogate for the active drug.

Data compiled from 4 studies revealed that men had a higher plasma clearance than women (1025 ml/min vs 828 ml/min) and a larger Vd (187 liters vs 160 liters). Dosing by body surface area will likely reduce that difference. No effect of age on the pharmacokinetics of topotecan was observed.

Therapeutic efficacy

The phase II/III ovarian carcinoma programme included one paclitaxel comparative trial; study 039, and 3 non-comparative trials; studies 012, 033, 034. All these studies were conducted accordance with Good Clinical Practices and provided reliable data on anti-tumour activity. In the topotecan treatment groups, there were altogether 445 women with advanced ovarian carcinoma who had failed cisplatin, or cisplatin and paclitaxel (study 033) based chemotherapy. In all studies, topotecan was administered as a 30-minute infusion of 1.5 mg/m^2/day on 5 consecutive days every 21 days. Dose adjustments were allowed within the range of 1.0-2.0 mg/m^2/day. In patients developing neutropenia, G-CSF was to be administered before a dose reduction was considered. The protocols of the four trials were similar with respect to evaluation of tumour response and other efficacy and safety variables. In study 039, the licensed dose of paclitaxel was used, a 3-hour infusion of 175 mg/m^2/day every 21 days, which could be modified in the range of 135-175 mg/m^2/day.

Study 039 was an open-label, multicentre, stratified phase III trial where ovarian-carcinoma patients who had failed one platinum-based regimen were randomised to receive topotecan or paclitaxel. If the disease progressed on randomised therapy, crossover to the alternate arm was allowed. The trial was

initiated in February 1994, the last patient was randomised on 31 January 1995 and the original study report was dated June 1995. Data updates of November 1995 and March 1996 have been submitted.

Altogether 235 patients were entered into the study, but 9 of them did not receive study medication. Thus, 226 patients of whom 112 were randomised to the topotecan arm, receiving a total of 555 courses and 114 to the paclitaxel arm, given a total of 550 courses were included in the overall analyses. Patients were stratified according to platinum-sensitivity, baseline ascites and age.

The primary objectives were to evaluate tumour response rate, based on the intent-to-treat (ITT) approach, the duration of the response, time to progression (time elapsed from first dose administered until the first documented disease progression) as well as qualitative and quantitative toxicities of topotecan. The secondary objectives were time to response, survival and effects on Quality of Life (QoL), which were repeatedly evaluated by using a questionnaire from the European Organisation for Research and Treatment of Cancer (QLQ-C30). In respect of safety, deaths, serious adverse events, qualitative and quantitative haematological and non-haematological toxicities, changes in vital signs, ECG measurements, bodyweight changes, and non-haematological laboratory parameters were monitored.

In the randomised phase, the overall response rate was 23/112 (20.5%; 95% CI 13; 28) and 16/114 (14%; 95% CI 8; 20), topotecan and paclitaxel, respectively. At the November 1995 data update, the median time to progressive disease was 19 and 15 weeks, in the topotecan and paclitaxel groups respectively (hazard ratio 0.7, p=0.053). After the latest update in March 1996, the survival data were considered as 'mature', with a median of 62 and 53 weeks, in the topotecan and paclitaxel groups respectively (hazard ratio 0.9, p=0.56).

There was a clear relationship between platinum-sensitivity and response rate in both treatment groups. In platinum-resistant (refractory+early relapse) patients, the response rate was lower, 4/40 (topotecan) and 2/43 (paclitaxel) and time to progression shorter. A higher response rate correlated with better performance status, absence of ascites and small tumour burden. No attempts were made to measure symptom reduction or delay in symptomatic progression following topotecan treatment, and QoL measures were not different between groups.

A total of 60 patients switched from paclitaxel to topotecan and 48 from topotecan to paclitaxel. The response rates after alternate therapy were low (6/60 [10%; 95% CI 4; 21] for topotecan and 2/48 [4%; 95% CI 0.5; 14] for paclitaxel).

Study 034 was an open-label, multicentre non-comparative phase II trial conducted in ovarian-carcinoma patients who had failed first-line platinum-based therapy. Altogether 111 patients, receiving a total of 552 courses, entered the study. At data cut-off, 90 patients had completed therapy and 18 had withdrawn, mainly due to adverse events.

The overall response rate was 16/111 (14%; 95% CI 8; 21), and in patients defined as platinum-resistant (refractory+early relapse) 2/53. The medians [ranges] of time to response, time to progression, response duration and overall survival were 10 [3-31] weeks, 11 [0.7-72] weeks, 16 [5-42] weeks and 1 year [1.4-72 weeks], respectively.

Study 033 was an open-label, multicentre non-comparative phase II trial. Two groups of ovarian-carcinoma patients were eligible: patients failing first-line therapy including paclitaxel and cis/carbo-platin, and patients failing 2 regimens of which paclitaxel and cis/carbo-platin must have been a component of one or both regimens. Altogether 139 women, 62 failing first-line therapy and 77 failing second-line therapy, received a total of 784 courses. At data cut-off in November 1995, 46% of patients were dead, 14 were still in therapy and 8 had withdrawn due to adverse events.

The overall response rate was 8/62 (13%; 95% CI 6;24) and 13/77 (17%; 95% CI 9;27) in patients failing first or second line treatment, respectively. The median time to progression was 17 and 11 weeks, respectively, and the overall survival was 45-46 weeks.

Study 012 was an open, non-comparative single centre phase II trial conducted in ovarian-carcinoma patients who had failed first-line platinum-based therapy. Altogether 30 patients were enrolled in the study, 8 were excluded from the per protocol analyses due to protocol violations. The overall response rate was 4/30 (13%) with a mean duration of 35-39 weeks, although there were no complete responses.

Safety

The clinical safety assessment of topotecan is based on the 4 phase II/III studies in patients with advanced ovarian carcinoma presented above. A total of 445 women with advanced ovarian carcinoma received 2019 courses of topotecan by June 1995 clinical cut-off. Supportive data originate from 8 finally reported or ongoing phase II studies in other patient groups given the dosing schedule applied for.

Deaths within 30 days of therapy are displayed in Table 1 based on updated information as at November 1995 clinical cut-off. In the comparative trial 039, a higher incidence of deaths was evident in the topotecan arm vs the paclitaxel arm which were a cause of concern. However, in the whole ovarian carcinoma programme, the incidence of deaths was lower and essentially similar to published data with respect to paclitaxel. Individual case reports support the notion that most deaths were related to progressive disease.

The number of withdrawals due to adverse experiences is displayed in Table 1. The most common reasons for the 35 withdrawals in the topotecan groups were 9 cases of thrombocytopenia, 4 cases of granulocytopenia and 4 cases of sepsis. **Table 1**

Study	**012**	**033**	**034**	**039**				*Total*
				randomised		*alternate*		
treatment	*topotecan*	*topotecan*	*topotecan*	*topotecan*	*paclitaxel*	*topotecan*	*paclitaxel*	
No. of patients	30	139	111	112	114	60	48	452*
No. of patients who died	0	8	8	11	3	5	5	32*
Withdrawal due to adverse experiences	1	8	10	13	8	3	2	35

* the total number includes patients receiving alternate topotecan treatment

The major target organ for toxicity was the bone marrow. Neutropenia with or without associated infection/fever and partly thrombocytopenia were dose limiting. Due to dose reduction, use of G-CSF and selection of patients, the myelotoxicity decreased with time. In the treated ovarian carcinoma population, grade 4 neutropenia was observed in 60% and 28% of patients during courses 1 and 6, respectively. The percentage of courses with grade 4 neutropenia was 42%. The percentage of patients with grade 4 neutropenia lasting beyond 7 days was similar over courses 1-6, occurring in 12.5% of courses. During course 1 of the comparative trial 039, grade 4 neutropenia was seen in 57% (63/111) of topotecan-treated patients vs 7% (8/112) of the paclitaxel group. During the same course, grade 4 neutropenia lasting for >7 days occurred in 21% of topotecan- vs 0.9% paclitaxel-treated patients.

In the overall ovarian population, the incidence of thrombocytopenia was 18% (course 1) but decreased to 2.5% (course 3). In the comparative trial 039, thrombocytopenia and subsequent purpura were more frequent in the topotecan arm than in the paclitaxel arm; thrombocytopenia grades 3/4 were reported in 18%/18% vs 0.9%/0% of patients, respectively. Anaemia, although more difficult to evaluate due to long-lasting effects of transfusion/slow cell turnover, had a higher incidence following topotecan- than paclitaxel treatment (40% vs 16%).

Clinical sequalae of myelotoxicity; fever, infection and sepsis as well as the use of systemic antibiotics were reported with a higher incidence in the topotecan- than in the paclitaxel arm. For instance, during course 1 of the comparative trial 039, infection ≥ grade 2 combined with neutropenia ≥ grade 4 were observed in 11% topotecan-treated patients vs 2% in the paclitaxel group. Intravenous antibiotics were used in 7% of the topotecan courses vs 0.5% of the paclitaxel courses. There was also a higher number of dosing delays, dose reductions and withdrawals associated with topotecan.

In the overall ovarian carcinoma population, non-haematological adverse events of grades 3 and 4 were experienced by 47% (210/445) of patients treated with topotecan. Nausea, vomiting, gastro-intestinal adverse reactions and asthenia/fatigue were most commonly reported. In the comparative trial 039, these adverse events were more frequent in the topotecan- than in the paclitaxel group. In contrast, topotecan caused less alopecia than paclitaxel and was not associated with hypersensitivity or neuropathy while grades 3/4 myalgia/arthalgia were reported in 2.6% of patients in the paclitaxel arm.

There were no indications of cumulative toxicity over time with respect of bone marrow, liver or kidneys. Furthermore, the toxicity profile was similar in platinum-resistant patients and the overall population. Patients with decreased performance status and possibly those heavily pretreated with chemotherapy pose a moderately increased risk for infectious complications.

In summary Basic pharmacokinetic properties, such as clearance, Vd and protein binding have been determined for both the pharmacologically active lactone and total topotecan, which includes the inactive carboxylate form. However, the elimination of topotecan has only been partly elucidated. Excretion data are very limited, and metabolism has only been studied *in vitro* except for the conversion of topotecan to the inactive carboxylate form. Adequate dose recommendations can not be given for patients with hepatic or severe renal impairment due to lack of data from these patient groups. Body surface area, renal function and performance status were identified as factors for prediction of exposure and toxicity in individual patients.

The dosage proposed for licensing, 1.5 mg/m^2/day for 5 consecutive days every 21 days, was identified in conventionally designed phase I MTD studies. No further attempts were made to define the optimum dose.

Across the study programme, antitumour activity similar to that of paclitaxel has been demonstrated. In the direct comparative study 039, time to progressive disease was borderline significantly prolonged in the topotecan group. Reduced performance status, bulky disease and non-response to previous therapy correlated with reduced antitumour activity.

The principle and dose-limiting toxicity of topotecan was confined to severe but reversible bone marrow suppression. In addition nausea, vomiting as well as gastrointestinal adverse reactions asthenia/fatigue was seen in notable frequency and intensity.

Benefit/risk assessment

Relapsing, metastatic ovarian carcinoma is a highly symptomatic and ultimately fatal disease where the reduction of tumour burden is considered to be associated with palliative effects of relevance to the patient. The anti-tumour activity of topotecan in these patients, failing therapy with cisplatin + paclitaxel and other cisplatin based treatments has been shown to be of a degree similar to that of paclitaxel administered second-line to cisplatin. Thus, essentially based on consistently demonstrated anti-tumour activity in studies of high quality, beneficial effects of relevance are considered documented.

The toxicity profile of topotecan is predictable, but with respect to bone marrow suppression rather profound, especially in a therapy administered with palliative intent. However, given a high quality level of supportive measures and surveillance, these toxic effects are considered manageable and do not translate to an unacceptable morbidity. Therefore, it is concluded that the overall benefit/risk relationship for topotecan is similar to that of paclitaxel in this population of patients with a grave prognosis. It is also to be observed that in patients failing combined cisplatin and paclitaxel therapy, there are no licensed alternative therapies.

5. Overall conclusions and benefit/risk assessment

Topotecan is a semisynthetic structural analogue of the natural alkaloid camptothecin intended for the treatment of ovarian cancer.

Although additional information will have to be submitted with regards to chemical and pharmaceutical aspects, the data submitted are acceptable to ensure the quality of the product.

The preclinical aspects, as well as clinical efficacy and safety of topotecan have been adequately investigated and data generated in the studies supported the clinical use of topotecan in patients with advanced ovarian carcinoma.

The CPMP considered during the review process that the overall benefit/risk ratio for topotecan is similar to that of paclitaxel in this population of patients with a grave prognosis. Consequently, the CPMP gave a favourable Opinion for granting a Marketing Authorisation for the following indication:

Treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.

6. Update of the SPC on the prolonged use of topotecan.

Topotecan is indicated for next-line treatment of patients with recurrent ovarian carcinoma, i.e. a strictly palliative setting. From a clinical point of view and in general, palliative objectives imply that therapy should be individualised with respect to duration and dose intensity. In clinical practice and if there are no signs of cumulative, or major toxicity compromising quality of life, this means that treatment is continued until there are signs of disease progression. Cytotoxic chemotherapy is, however, always associated with toxicity of relevance.

The benefit of continued therapy could be determined based on randomised withdrawal of chemotherapy after, e.g. 6 cycles of therapy in patients with non-progressive disease. If there are no signs of cumulative toxicity or tolerability problems, this type of trials, however, are hard to conduct due to investigators' and patients' reluctance to stop a putatively beneficial treatment. In an attempt to address this issue, a retrospective analysis of patients with recurrent ovarian cancer treated with topotecan in mono-therapy of all 5 previously submitted studies was conducted.

This was a supplementary retrospective analysis to evaluate the benefit of topotecan administered over a prolonged period was conducted on 523 relapsed ovarian cancer patients. A total of 87 responses were observed in the studies, thereof 13 during cycles 5 and 6 and 3 after cycle 6. Overall response rates and survival were due to obvious reasons much worse in patients treated with ≤ 6 cycles ("lead time bias", early progressors cannot qualify for > 6 cycles of therapy). There were, however, 49 patients who ended therapy exactly at cycle 6 without signs of progressive disease and these patients were compared with those treated for 7 cycles or more. Median survival was apparently longer in patients treated for > 6 cycles.

Submitted analyses include comparisons between patients receiving 6 or fewer courses of therapy, more than 6 courses and within the group of patients receiving more than 6 courses, between courses 1-6 and >7. Altogether 371 patients received ≤6 cycles and 152 >6 cycles (46 >10 courses and 9 >20 cycles). In 91% of the patients receiving >6 cycles of therapy, treatment was withdrawn due to progressive disease vs. 80% of individuals treated with ≤ 6 cycles. As expected baseline performance status was better in those receiving >6 courses (PS 0: 53% vs. 38%), more patients showed late relapse to prior cisplatin therapy (40% vs. 30%), etc.

Despite the obvious weaknesses of the presented analyses, made evident by e.g. baseline differences, available data support the statement that there are no signs of cumulative toxicity and that therapy can be administered for prolonged periods of time, in practice until disease progression.

With respect to haematological toxicity, more patients in the ≤ 6-cycle group experienced grade 4 thrombocytopenia (25% vs. 13%), otherwise no differences of importance were observed, including the use of supportive measures (G-CSF, transfusions, etc.). As regards dose intensity, there were no major differences between groups. As regards non-haematological toxicity, numerically higher figures were reported in the ≤ 6-cycle group with respect to nausea, vomiting, infectious events, fatigue, etc. For the within group comparison, fewer events were reported during courses 7+ than during courses 1-6.

A total of 87 responses were observed in the studies, thereof 13 during cycles 5 and 6 and 3 after cycle 6. Overall response rates and survival were -due to obvious reasons- much worse in patients treated with ≤ 6 cycles ("lead time bias", early progressors cannot qualify for > 6 cycles of therapy). There were, however, 49 patients who ended therapy exactly at cycle 6 without signs of progressive disease and these patients were compared with those treated for 7 cycles or more. Median survival was apparently longer in patients treated for > 6 cycles. Due to likely confounders, submitted data cannot be interpreted as indicating that prolonged therapy causes prolonged survival. Trial conditions were reflected in the SPC.

7. Update of the SPC following the 6th PSUR

The following modifications to the SPC were implemented as requested from the CPMP as a result of the assessment of the sixth PSUR:

- Addition of the sentence: ”Hypersensitivity reactions, including rash, urticaria, angioedema and anaphylactic reactions have been reported rarely”.
- Deletion of the statement “No evidence of significant cardiotoxicity, neurotoxicity or other major toxicity was observed with topotecan”.

8. Renewal of Marketing Authorisation for Hycamtin (12 November 2001).

Following review of the renewal application, the SPC was amended with respect to:

- Section 4.5 Addition of information about the sequence dependent interaction with cisplatin
- Section 4.8: Immune System disorders: Addition of “urticaria, angioedema” as rare. Under the heading “General disorders and administration site conditions”, “extravasation” is stated as a rare event.