Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Topotecan 1 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 1 mg topotecan (as hydrochloride).

One vial of 1 ml of concentrate contains 1 mg topotecan (as hydrochloride).
One vial of 4 ml of concentrate contains 4 mg topotecan (as hydrochloride).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear yellow to yellow green colour solution, free from visible particles.

pH = 2.0-2.6.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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).

4.2 Posology and method of administration

Method of administration

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 (see section 6.6).

Topotecan must be further diluted before use (see section 6.6).

The diluted solution should be clear, colourless to light yellow colour, free from visible particles.

Posology

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 $\geq 1.5 \times 10^9$/l, a platelet count of $\geq 100 \times 10^9$/l and a haemoglobin level of ≥ 9 g/dl (after transfusion if necessary).

Ovarian and Small Cell Lung Carcinoma

Initial dose
The recommended dose of topotecan is 1.5 mg/m^2 body surface area/day administered by intravenous infusion over 30 minutes daily for five consecutive days with a three week interval between the start of each course. If well tolerated, treatment may continue until disease progression (see sections 4.8 and 5.1).

Subsequent doses
Topotecan should not be re-administered unless the neutrophil count is ≥ 1 x 10^9/l, the platelet count is ≥ 100 x 10^9/l, and the haemoglobin level is ≥ 9 g/dl (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer topotecan with other medicinal products (e.g. G-CSF) or to dose reduce to maintain neutrophil counts.

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count < 0.5 x 10^9/l) for seven days or more, or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, the dose should be reduced by 0.25 mg/m^2/day to 1.25 mg/m^2/day (or subsequently down to 1.0 mg/m^2/day if necessary)

Doses should be similarly reduced if the platelet count falls below 25 x 10^9/l. In clinical trials, topotecan was discontinued if the dose had been reduced to 1.0 mg/ m^2 and a further dose reduction was required to manage adverse effects.

Cervical Carcinoma

Initial dose
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 six courses or until progressive disease.

Subsequent doses
Topotecan should not be re-administered unless the neutrophil count is more than or equal to 1.5 x 10^9/l, the platelet count is more than or equal to 100 x 10^9/l, and the haemoglobin level is more than or equal to 9 g/dl (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer topotecan with other medicinal products (e.g. G-CSF) or to dose reduce to maintain neutrophil counts.

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count less than 0.5 x 10^9/l) for seven days or more, or severe neutropenia associated with fever or infection or who have had treatment delayed due to neutropenia, the dose should be reduced by 20% to 0.60 mg/ m^2/day for subsequent courses (or subsequently down to 0.45 mg/ m^2/day if necessary).

Doses should be similarly reduced if the platelet count falls below 25 x 10^9/l.

Dosage in renal impairment
Monotherapy (Ovarian and Small cell lung carcinoma)
Insufficient data are available to make a recommendation for patients with a creatinine clearance < 20 ml/min. Limited data indicate that the dose should be reduced in patients with moderate renal impairment. The recommended monotherapy dose of topotecan in patients with ovarian or small cell lung carcinoma and a creatinine clearance between 20 and 39 ml/min is 0.75 mg/ m^2/day for five consecutive days.

Combination therapy (Cervical carcinoma)
In clinical studies with topotecan in combination with cisplatin for the treatment of cervical cancer, therapy was only initiated in patients with serum creatinine less than or equal to 1.5 mg/dl. If, during topotecan/cisplatin combination therapy serum creatinine exceeds 1.5 mg/dl, it is recommended that the full prescribing information be consulted for any advice on cisplatin dose reduction/continuation. If cisplatin is discontinued, there are insufficient data regarding continuing monotherapy with topotecan in patients with cervical cancer.

Paediatric population
The experience in children is limited, therefore no recommendation for treatment of paediatric patients with topotecan can be given (see sections 5.1 and 5.2).

4.3 Contraindications

Topotecan is contraindicated in patients who
- have a history of severe hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- are breast feeding (see section 4.6)
- already have severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils < 1.5 x 10^9/l and/or a platelet count < 100 x 10^9/l.

4.4 Special warnings and precautions for use

Haematological toxicity
Haematological toxicity is dose-related and full blood count including platelets should be monitored regularly (see section 4.2).

Myelosuppression
As with other cytotoxic medicinal products, topotecan can cause severe myelosuppression. Myelosuppression leading to sepsis and fatalities due to sepsis have been reported in patients treated with topotecan (see section 4.8).

Neutropenia
Topotecan-induced neutropenia can cause neutropenic colitis. Fatalities due to neutropenic colitis have been reported in clinical trials with topotecan. In patients presenting with fever, neutropenia, and a compatible pattern of abdominal pain, the possibility of neutropenic colitis should be considered.

Interstitial lung disease
Topotecan has been associated with reports of interstitial lung disease (ILD), some of which have been fatal (see section 4.8). Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation and use of pneumotoxic substances and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms indicative of ILD (e.g. cough, fever, dyspnoea and/or hypoxia), and topotecan should be discontinued if a new diagnosis of ILD is confirmed.

Thrombocytopenia
Topotecan monotherapy and topotecan in combination with cisplatin are commonly associated with clinically relevant thrombocytopenia. This should be taken into account when prescribing topotecan e.g. in case patients at increased risk of tumour bleeds are considered for therapy.

As expected, patients with poor performance status (PS>1) have a lower response rate and an increased incidence of complications such as fever, infection and sepsis (see section 4.8). Accurate assessment of performance status at the time therapy is given is important, to ensure that patients have not deteriorated to performance status 3.

Renal and hepatic insufficiency
There is insufficient experience of the use of topotecan in patients with severely impaired renal function (creatinine clearance < 20 ml/min) or severely impaired hepatic function (serum bilirubin ≥ 10 mg/dl) due to cirrhosis. Topotecan is not recommended to be used in these patient groups.

A small number of hepatically impaired patients (serum bilirubin between 1.5 and 10 mg/dl) were given intravenous

topotecan at 1.5 mg/m^2 for five days every three weeks. A reduction in topotecan clearance was observed. However there are insufficient data available to make a dose recommendation for this patient group.

4.5 Interaction with other medicinal products and other forms of interaction

No *in vivo* human pharmacokinetic interaction studies have been performed.

Topotecan does not inhibit human P450 enzymes (see section 5.2). In an intravenous population study, the co-administration of granisetron, ondansetron, morphine or corticosteroids did not appear to have a significant effect on the pharmacokinetics of total topotecan (active and inactive form).

In combining topotecan with other chemotherapy agents, reduction of the doses of each medicinal product may be required to improve tolerability. However, in combining with platinum agents, there is a distinct sequence-dependent interaction depending on whether the platinum agent is given on day 1 or 5 of the topotecan dosing. If either cisplatin or carboplatin is given on day 1 of the topotecan dosing, a lower dose of each agent must be given to improve tolerability compared to the dose of each agent which can be given if the platinum agent is given on day 5 of the topotecan dosing.

When topotecan (0.75 mg/m^2/day for 5 consecutive days) and cisplatin (60 mg/m^2/day on Day 1) were administered in 13 patients with ovarian cancer, a slight increase in AUC (12%, n=9) and C_{max} (23%, n=11) was noted on day 5. This increase is considered unlikely to be of clinical relevance.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
As with all cytotoxic chemotherapy, effective contraceptive methods must be advised when either partner is treated with topotecan.

Women of childbearing potential
Topotecan has been shown to cause embryo-foetal lethality and malformations in preclinical studies (see section 5.3). As with other cytotoxic medicinal products, topotecan may cause foetal harm and therefore women of child bearing potential should be advised to avoid becoming pregnant during therapy with topotecan.

Pregnancy
If topotecan is used during pregnancy, or if the patient becomes pregnant during therapy with topotecan, the patient must be warned of the potential hazards to the foetus.

Breastfeeding
Topotecan is contra-indicated during breast-feeding (see section 4.3). Although it is not known whether topotecan is excreted in human breast milk, breast-feeding should be discontinued at the start of therapy.

Fertility
No effects on male or female fertility have been observed in reproductive toxicity studies in rats (see section 5.3). However as with other cytotoxic medicinal products topotecan is genotoxic and effects on fertility, including male fertility, cannot be excluded.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, caution should be observed when driving or operating machines if fatigue and asthenia persist.

4.8 Undesirable effects

In dose-finding trials involving 523 patients with relapsed ovarian cancer and 631 patients with relapsed small cell lung cancer, the dose limiting toxicity of topotecan monotherapy was found to be haematological. Toxicity was predictable and reversible. There were no signs of cumulative haematological or non- haematological toxicity.

The adverse event profile for topotecan when given in combination with cisplatin in the cervical cancer clinical trials is consistent with that seen with topotecan monotherapy. The overall haematological toxicity is lower in patients treated with topotecan in combination with cisplatin compared to topotecan monotherapy, but higher than with cisplatin alone.

Additional adverse events were seen when topotecan was given in combination with cisplatin, however, these events were seen with cisplatin monotherapy and not attributable to topotecan. The prescribing information for cisplatin should be consulted for a full list of adverse events associated cisplatin use.

The integrated safety data for topotecan monotherapy are presented below.

Adverse reactions are listed below, by system organ class and absolute frequency (all reported events). Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders
Very common: febrile neutropenia, neutropenia (see Gastrointestinal disorders), thrombocytopenia, anaemia, leucopenia.
Common: pancytopenia
Not known: severe bleeding (associated with thrombocytopenia)

Respiratory, thoracic and mediastinal disorders
Rare: interstitial lung disease (some cases have been fatal).

Gastrointestinal disorders
Very common: nausea, vomiting and diarrhoea (all of which may be severe), constipation, abdominal pain[1], mucositis
[1]Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see section 4.4).

Skin and subcutaneous tissue disorders
Very common: alopecia.
Common: pruritus.

Metabolism and nutrition disorders
Very common: anorexia (which may be severe).

Infections and infestations
Very common: infection.
Common: sepsis[2].
[2]Fatalities due to sepsis have been reported in patients treated with topotecan (see section 4.4).

General disorders and administration site conditions
Very common: pyrexia, asthenia, fatigue.
Common: malaise.
Very rare: extravasation[3]
[3]Extravasation has been reported very rarely. Reactions have been mild and have not generally required specific therapy.

Immune system disorders
Common: hypersensitivity reaction including rash.
Rare: anaphylactic reaction, angioedema, urticaria.

Hepato-biliary disorders
Common: hyperbilirubinaemia.

The incidence of adverse events listed above have the potential to occur with a higher frequency in patients who have a poor performance status (see section 4.4).

The frequencies associated with the haematological and non-haematological adverse events listed below represent the adverse event reports considered to be related/possibly related to topotecan therapy.

Haematological
Neutropenia: Severe (neutrophil count < 0.5 x 10^9/l) during course 1 was seen in 55 % of the patients and with duration ≥ seven days in 20 % and overall in 77 % of patients (39 % of courses). In association with severe neutropenia, fever or infection occurred in 16 % of patients during course 1 and overall in 23 % of patients (6 % of courses). Median time to onset of severe neutropenia was nine days and the median duration was seven days. Severe neutropenia lasted beyond seven days in 11 % of courses overall. Among all patients treated in clinical trials (including both those with severe neutropenia and those who did not develop severe neutropenia), 11 % (4 % of courses) developed fever and 26 % (9 % of courses) developed infection. In addition, 5 % of all patients treated (1 % of courses) developed sepsis (see section 4.4).

Thrombocytopenia: Severe (platelets less than 25 x 10^9/l) in 25 % of patients (8 % of courses); moderate (platelets between 25.0 and 50.0 x 10^9/l) in 25 % of patients (15 % of courses). Median time to onset of severe thrombocytopenia was Day 15 and the median duration was five days. Platelet transfusions were given in 4 % of courses. Reports of significant sequelae associated with thrombocytopenia including fatalities due to tumour bleeds have been infrequent.

Anaemia: Moderate to severe (Hb ≤ 8.0 g/dl) in 37 % of patients (14 % of courses). Red cell transfusions were given in 52 % of patients (21 % of courses).

Non-haematological
Frequently reported non-haematological effects were gastrointestinal such as nausea (52 %), vomiting (32 %), and diarrhoea (18 %), constipation (9 %) and mucositis (14 %). Severe (grade 3 or 4) nausea, vomiting, diarrhoea and mucositis incidence was 4, 3, 2 and 1 % respectively.

Mild abdominal pain was also reported amongst 4 % of patients.

Fatigue was observed in approximately 25 % and asthenia in 16 % of patients whilst receiving topotecan. Severe (grade 3 or 4) fatigue and asthenia incidence was 3 and 3 % respectively.

Total or pronounced alopecia was observed in 30 % of patients and partial alopecia in 15 % of patients.

Other severe events occurring in patients that were recorded as related or possibly related to topotecan treatment were anorexia (12 %), malaise (3 %) and hyperbilirubinaemia (1 %).

Hypersensitivity reactions including rash, urticaria, angioedema and anaphylactic reactions have been reported rarely. In clinical trials, rash was reported in 4 % of patients and pruritus in 1.5 % of patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via ‘freepost’, in addition to the traditional post-paid ‘yellow card’ option. FREEPOST, Pharmacovigilance Section, Irish Medicines Board, Kevin O’Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: +353 1

6764971 Fax: +353 1 6762517. Website: www.imb.ie e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

There is no known antidote for topotecan overdose. The primary complications of overdose are anticipated to be bone marrow suppression and mucositis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The anti-tumour activity of topotecan involves the inhibition of topoisomerase-I, an enzyme intimately involved in DNA replication as it relieves the torsional strain introduced ahead of the moving replication fork. Topotecan inhibits topoisomerase-I by stabilising the covalent complex of enzyme and strand-cleaved DNA which is an intermediate of the catalytic mechanism. The cellular sequela of inhibition of topoisomerase-I by topotecan is the induction of protein-associated DNA single-strand breaks.

Relapsed Ovarian Cancer

In a comparative study of topotecan and paclitaxel in patients previously treated for ovarian carcinoma with platinum based chemotherapy (n = 112 and 114, respectively), the response rate (95 % CI) was 20.5 % (13 %, 28 %) versus 14 % (8 %, 20 %) and median time to progression 19 weeks versus 15 weeks (hazard ratio 0.7 [0.6, 1.0]), for topotecan and paclitaxel, respectively. Median overall survival was 62 weeks for topotecan versus 53 weeks for paclitaxel (hazard ratio 0.9 [0.6, 1.3]).

The response rate in the whole ovarian carcinoma programme (n = 392, all previously treated with cisplatin or cisplatin and paclitaxel) was 16 %. The median time to response in clinical trials was 7.6-11.6 weeks. In patients refractory to, or relapsing within 3 months after cisplatin therapy (n = 186), the response rate was 10%.

These data should be evaluated in the context of the overall safety profile of the medicinal product, in particular to the important haematological toxicity (see section 4.8).

A supplementary retrospective analysis was conducted on data from 523 patients with relapsed ovarian cancer. Altogether, 87 complete and partial responses were observed, with 13 of these occurring during cycles 5 and 6 and 3 occurring thereafter. For patients administered more than 6 cycles of therapy, 91 % completed the study as planned or were treated until disease progression with only 3 % withdrawn for adverse events.

Relapsed SCLC

A phase III trial (study 478) compared oral topotecan plus Best Supportive Care (BSC) (n=71) with BSC alone (n=70) in patients who had relapsed following first line therapy (median time to progression [TTP] from first-line therapy: 84 days for oral topotecan + BSC, 90 days for BSC) and for whom retreatment with intravenous chemotherapy was not considered appropriate. Oral topotecan plus BSC group had a statistically significant improvement in overall survival compared with the BSC alone group (Log- rank p=0.0104). The unadjusted hazard ratio for oral topotecan plus BSC group relative to BSC alone group was 0.64 (95 % CI: 0.45, 0.90). The median survival for patients treated with topotecan + BSC was 25.9 weeks (95 % C.I. 18.3, 31.6) compared to 13.9 weeks (95 % C.I. 11.1, 18.6) for patients receiving BSC alone (p=0.0104).

Patient self-reports of symptoms using an unblinded assessment showed a consistent trend for symptom benefit for oral topotecan + BSC.

One Phase 2 study (Study 065) and one Phase 3 study (Study 396) were conducted to evaluate the efficacy of oral topotecan versus intravenous topotecan in patients who had relapsed ≥ 90 days after completion of one prior regimen of chemotherapy (see Table 1). Oral and intravenous topotecan were associated with similar symptom palliation in

patients with relapsed sensitive SCLC in patient self reports on an unblinded symptom scale assessment in each of these two studies.

Table 1. Summary of survival, response rate, and time to progression in SCLC patients treated with oral topotecan or intravenous topotecan

	Study 065		**Study 396**	
	Oral topotecan	**Intravenous** topotecan	**Oral** topotecan	**Intravenous** topotecan
	(N = 52)	**(N = 54)**	**(N = 153)**	**(N = 151)**
Median survival (weeks) (95% CI)	32.3 (26.3,40.9)	25.1 (21.1, 33.0)	33.0 (29.1, 42.4)	35.0 (31.0, 37.1)
Hazard ratio (95%CI)	0.88 (0.59, 1.31)		0.88 (0.7, 1.11)	
Response rate (%) (95% CI)	23.1 (11.6, 34.5)	14.8 (5.3, 24.3)	18.3 (12.2, 24.4)	21.9 (15.3, 28.5)
Difference in response rate (95% CI)	8.3 (-6.6, 23.1)		-3.6 (-12.6, 5.5)	
Median time to progression (weeks) (95% CI)	14.9 (8.3, 21.3)	13.1 (11.6, 18.3)	11.9 (9.7, 14.1)	14.6 (13.3, 18.9)
Hazard ratio (95% CI)	0.90 (0.60, 1.35)		1.21 (0.96, 1.53)	

N = total number of patients treated.
CI = Confidence interval.

In another randomised phase III trial which compared IV topotecan to cyclophosphamide, Adriamycin (doxorubicin) and vincristine (CAV) in patients with relapsed, sensitive SCLC, the overall response rate was 24.3 % for topotecan compared to 18.3 % for the CAV group. Median time to progression was similar in the two groups (13.3 weeks and 12.3 weeks respectively). Median survivals for the two groups were 25.0 and 24.7 weeks respectively. The hazard ratio for survival of IV topotecan relative to CAV was 1.04 (95 % CI 0.78 – 1.40).

The response rate to topotecan in the combined small cell lung cancer programme(n=480) for patients with relapsed disease sensitive to first-line therapy, was 20.2 %. The median survival was 30.3 weeks (95 % CI: 27.6, 33.4).

In a population of patients with refractory SCLC (those not responding to first line therapy), the response rate to topotecan was 4.0 %.

Cervical Carcinoma

In a randomised, comparative phase III trial conducted by the Gynaecological Oncology Group (GOG 0179), topotecan plus cisplatin (n = 147) was compared with cisplatin alone (n = 146) for the treatment of histologically confirmed persistent, recurrent or Stage IVB carcinoma of the cervix where curative treatment with surgery and/or radiation was not considered appropriate. Topotecan plus cisplatin had a statistically significant benefit in overall survival relative to cisplatin monotherapy after adjusting for interim analyses (Log-rank p = 0.033).

Table 2: Study results Study GOG-0179

ITT population		
	Cisplatin 50 mg/m^2 d. 1 q2l d.	**Cisplatin 50 mg/m^2 d. 1 + Topotecan 0.75 mg/m^2 dx3 q21**
Survival (months)	**(n = 146)**	**(n = 147)**
Median (95% C.I.)	6.5 (5.8, 8.8)	9.4 (7.9, 11.9)

Hazard ratio (95% C.I.)	0.76 (0.59-0.98)	
Log rank p-value	0.033	
Patients without Prior Cisplatin Chemoradiotherapy		
	Cisplatin	**Topotecan/Cisplatin**
Survival (months)	**(n = 46)**	**(n = 44)**
Median (95% C.I.)	8.8 (6.4, 11.5)	15.7 (11.9, 17.7)
Hazard ratio (95% C.I.)	0.51 (0.31, 0.82)	
Patients with Prior Cisplatin Chemoradiotherapy		
	Cisplatin	**Topotecan/Cisplatin**
Survival (months)	**(n = 72)**	**(n = 69)**
Median (95% C.I.)	5.9 (4.7, 8.8)	7.9 (5.5, 10.9)
Hazard ratio (95% C.I.)	0.85 (0.59, 1.21)	

In patients (n = 39) with recurrence within 180 days after chemoradiotherapy with cisplatin, the median survival in the topotecan plus cisplatin arm was 4.6 months (95 % C.I.: 2, 6, 6.1) versus 4.5 months (95 % C.I.: 2.9, 9.6) for the cisplatin arm with an hazard ratio of 1.15 (0.59, 2.23). In those (n = 102) with recurrence after 180 days, the median survival in the topotecan plus cisplatin arm was 9.9 months (95 % C.I.: 7, 12.6) versus 6.3 months (95 % C.I.: 4.9, 9.5) for the cisplatin arm with an hazard ratio of 0.75 (0.49, 1.16).

Paediatric population

Topotecan was also evaluated in the paediatric population; however, only limited data on efficacy and safety are available.

In an open-label trial involving children (n = 108, age range: infant to 16 years) with recurrent or progressive solid tumours, topotecan, was administered at a starting dose of 2.0 mg/m^2 given as a 30- minute infusion for 5 days repeated every 3 weeks for up to one year depending on response to therapy. Tumour types included were Ewing's Sarcoma/primitive neuroectodermal tumour, neuroblastoma, osteoblastoma, and rhabdomyosarcoma. Antitumour activity was demonstrated primarily in patients with neuroblastoma. Toxicities of topotecan in paediatric patients with recurrent and refractory solid tumours were similar to those historically seen in adult patients. In this study, forty-six (43 %) patients received G-CSF over 192 (42.1 %) courses; sixty-five (60 %) received transfusions of Packed Red Blood Cells and fifty (46 %) of platelets over 139 and 159 courses (30.5 % and 34.9 %) respectively. Based on the dose- limiting toxicity of myelosuppression, the maximum tolerated dose (MTD) was established at 2.0 mg/m^2/day with G-CSF and 1.4 mg/m^2/day without G-CSF in a pharmacokinetic study in paediatric patients with refractory solid tumours (see section 5.2).

5.2 Pharmacokinetic properties

Following intravenous administration of topotecan at doses of 0.5 to 1.5 mg/m^2 as a 30 minute infusion daily for five days, topotecan demonstrated a high plasma clearance of 62 l/h (SD 22), corresponding to approximately 2/3 of liver blood flow. Topotecan also had a high volume of distribution, about 132 1, (SD 57) and a relatively short half-life of 2-3 hours. Comparison of pharmacokinetic parameters did not suggest any change in pharmacokinetics over the 5 days of dosing. Area under the curve increased approximately in proportion to the increase in dose. There is little or no accumulation of topotecan with repeated daily dosing and there is no evidence of a change in the PK after multiple doses. Preclinical studies indicate plasma protein binding of topotecan is low (35 %) and distribution between blood cells and plasma was fairly homogeneous.

The elimination of topotecan has only been partly investigated in man. A major route of clearance of topotecan was by hydrolysis of the lactone ring to form the ring-opened carboxylate.

Metabolism accounts for <10 % of the elimination of topotecan. An N-desmethyl metabolite, which was shown to have similar or less activity than the parent in a cell-based assay, was found in urine, plasma, and faeces. The mean

metabolite: parent AUC ratio was less than 10% for both total topotecan and topotecan lactone. An O-glucuronidation metabolite of topotecan and N-desmethyl topotecan has been identified in the urine.

Overall recovery of medicinal product-related material following five daily doses of topotecan was 71 to 76 % of the administered IV dose. Approximately 51 % was excreted as total topotecan and 3% was excreted as N-desmethyl topotecan in the urine. Faecal elimination of total topotecan accounted for 18% while faecal elimination of N-desmethyl topotecan was 1.7 %. Overall, the N-desmethyl metabolite contributed a mean of less than 7% (range 4-9%) of the total medicinal product related material accounted for in the urine and faeces. The topotecan-O-glucuronide and N-desmethyl topotecan-O-glucuronide in the urine were less than 2.0%.

In vitro data using human liver microsomes indicate the formation of small amounts of N-demethylated topotecan. In vitro, topotecan did not inhibit human P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, of CYP4A nor did it inhibit the human cytosolic enzymes dihydropyrimidine or xanthine oxidase.

When given in combination with cisplatin (cisplatin day 1, topotecan days 1 to 5), the clearance of topotecan was reduced on day 5 compared to day 1 (19.1 l/h/m^2 compared to 21.3 l/h/m^2 [n = 9]) (see section 4.5).

Plasma clearance in patients with hepatic impairment (serum bilirubin between 1.5 and 10 mg/dl) decreased to about 67 % when compared with a control group of patients. Topotecan half-life was increased by about 30% but no clear change in volume of distribution was observed. Plasma clearance of total topotecan (active and inactive form) in patients with hepatic impairment only decreased by about 10 % compared with the control group of patients.

Plasma clearance in patients with renal impairment (creatinine clearance 41-60 ml/min.) decreased to about 67 % compared with control patients. Volume of distribution was slightly decreased and thus half-life only increased by 14 %. In patients with moderate renal impairment topotecan plasma clearance was reduced to 34 % of the value in control patients. Mean half-life increased from 1.9 hours to 4.9 hours.

In a population study, a number of factors including age, weight and ascites had no significant effect on clearance of total topotecan (active and inactive form).

Paediatric population

The pharmacokinetics of topotecan given as a 30-minute infusion for 5 days were evaluated in two studies. One study included a dose range of 1.4 mg/m^2 to 2.4 mg/m^2 in children (aged 2 up to 12 years, n = 18), adolescents (aged 12 up to 16 years, n = 9), and young adults (aged 16 to 21 years, n = 9) with refractory solid tumours. The second study included a dose range of 2.0 mg/m^2 to 5.2 mg/m^2 in children (n = 8), adolescents (n = 3), and young adults (n = 3) with leukemia. In these studies, there were no apparent differences in the pharmacokinetics of topotecan among children, adolescents, and young adult patients with solid tumours or leukaemia, but data are too limited to draw definite conclusions.

5.3 Preclinical safety data

Resulting from its mechanism of action, topotecan is genotoxic to mammalian cells (mouse lymphoma cells and human lymphocytes) *in vitro* and mouse bone marrow cells *in vivo*. Topotecan was also shown to cause embryo-foetal lethality when given to rats and rabbits.

In reproductive toxicity studies with topotecan in rats there was no effect on male or female fertility;
however, in females super-ovulation and slightly increased pre-implantation loss were observed. The carcinogenic potential of topotecan has not been studied.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartaric acid (E334)
Hydrochloric acid (E507) (for pH adjustment)
Sodium hydroxide (E524) (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Vial before opening
24 months.

Chemical and physical in-use stability has been demonstrated for 10 days at 2-8°C and 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless dilution has taken has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

2 ml colorless, Type I glass vial, closed with a 13 mm flurotec rubber stopper and sealed with an flip-off aluminium seal containing 1 ml of concentrate.

6 ml colorless, Type I glass vial, closed with a 20 mm flurotec rubber stopper and sealed with an flip-off aluminium seal containing 4 ml of concentrate.

Topotecan is available in cartons containing 1 x 1 ml, 5 x 1 ml, 1 x 4 ml and 5 x 4 ml vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

General precautions
The normal procedures for proper handling and disposal of anticancer medicinal products should be adopted, namely:
- Personnel should be trained to dilute the medicinal product.
- Pregnant staff should be excluded from working with this medicinal product.
- Personnel handling this medicinal product during dilution should wear protective clothing including mask, goggles and gloves.
- All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.

Instructions for dilution
The concentrate is clear yellow to yellow green in colour and contains 1 mg per ml of topotecan. Further dilution of the appropriate volume of the concentrate with either sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection to reach a final topotecan concentration of between 25 and 50 microgram/ml in the solution for infusion.

The diluted solution should be clear, colourless to light yellow colour, free from visible particles.

Disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Oncology Plc
Lion Court
Farnham Road
Bordon
Hampshire GU35 0NF
United Kingdom

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10 DATE OF REVISION OF THE TEXT