1. NAME OF THE MEDICINAL PRODUCT

HYCAMTIN 0.25 mg
HYCAMTIN 1 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HYCAMTIN 0.25 mg

Each capsule contains 0.25 mg of topotecan. (as hydrochloride).

HYCAMTIN 1 mg

Each capsule contains 1 mg of topotecan. (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin capsule.

HYCAMTIN 0.25 mg hard gelatin capsules

The capsules are, opaque, white to yellowish white and imprinted with “HYCAMTIN” and “0.25 mg’.

HYCAMTIN 1 mg hard gelatin capsules
The capsules are opaque, pink and imprinted with “HYCAMTIN” and “1 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HYCAMTIN capsules are 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).

4.2 Posology and method of administration

HYCAMTIN capsules should only be prescribed and therapy supervised by a physician experienced in the use of chemotherapeutic agents.

Posology
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).

Initial dose
The recommended dose of HYCAMTIN capsules is 2.3 mg/m^2 body surface area per day administered 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).

The capsule(s) must be swallowed whole, and must not be chewed crushed or divided.
Hycamtin capsules may be taken with or without food (see section 5.2).

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 reduce the dose 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 0.4 mg/m^2/day to 1.9 mg/m^2/day (or subsequently down to 1.5 mg/m^2/day if necessary).

Doses should be similarly reduced if the platelet count falls below 25 x 10^9/l. In clinical studies, topotecan was discontinued if the dose needed to be reduced below 1.5 mg/m^2 /day.

For patients who experience Grade 3 or 4 diarrhoea, the dose should be reduced by 0.4 mg/m^2/day for subsequent courses (see section 4.4). Patients with Grade 2 diarrhoea may need to follow the same dose modification guidelines.

Proactive management of diarrhoea with anti-diarrhoeal agents is important. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, and interruption of topotecan therapy (see sections 4.4 and 4.8).

Special populations
Patients with renal impairment
The recommended monotherapy dose of oral topotecan in patients with small cell lung carcinoma with creatinine clearance between 30 and 49 ml/min is 1.9 mg/m^2/day for five consecutive days. If well tolerated, the dose may be increased to 2.3 mg/m^2/day in subsequent cycles (see section 5.2).

Limited data in Korean patients with creatinine clearance less than 50 ml/min suggest a further lowering of dose may be required (see section 5.2).

Insufficient data are available to make a recommendation for patients with a creatinine clearance < 30 ml/min.

Patients with hepatic impairment
Pharmacokinetics of HYCAMTIN capsules have not been specifically studied in patients with impaired hepatic function. There are insufficient data available with HYCAMTIN capsules to make a dose recommendation for this patient group (see section 4.4).

Paediatric population
Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly No overall differences in effectiveness were observed between patients aged over 65 years and younger adult patients. However in the two studies in which both oral and intravenous topotecan were administered, patients over 65 years old receiving oral topotecan experienced an increase in drug related diarrhoea compared to those younger than 65 years of age (see section 4.4 and 4.8).

4.3 Contraindications

- Severe hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Breast-feeding (see section 4.6)
- Severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils < 1.5 x 10^9/l and/or a platelet count of < 100 x 10^9/l.

4.4 Special warnings and precautions for use

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

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).

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

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.

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

As would be 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 PS 3.

Topotecan is partly eliminated via renal excretion and renal impairment might lead to increased exposure to topotecan. Dosing recommendations for patients receiving oral topotecan with creatinine clearance less than 30 ml/min have not been established. Use of topotecan in these patients is not recommended (see section 4.2).

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 /day 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. There is insufficient experience of the use of topotecan in patients with severely impaired hepatic function (serum bilirubin ≥ 10 mg/dl). Use of topotecan in these patients is not recommended (see section 4.2)..

Diarrhoea, including severe diarrhoea requiring hospitalization, has been reported during treatment with oral topotecan. Diarrhoea related to oral topotecan can occur at the same time as drug-related neutropenia and its sequelae. Communication with patients prior to drug administration regarding these side effects and proactive management of early and all signs and symptoms of diarrhoea is important. Cancer treatment-induced diarrhoea (CTID) is associated with significant morbidity and may be life-threatening. Should diarrhoea occur during treatment with oral topotecan, physicians are advised to aggressively manage diarrhoea. Clinical guidelines describing the aggressive management of CTID include specific recommendations on patient communication and awareness, recognition of early warning signs, use of anti-diarrhoeals and antibiotics, changes in fluid intake and diet, and need for hospitalization (see sections 4.2 and 4.8).

Intravenous topotecan should be considered in the following clinical situations: uncontrolled emesis, swallowing disorders, uncontrolled diarrhoea, clinical conditions and medication that may alter gastrointestinal motility and drug absorption.

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 a population study using the intravenous route, 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).

Topotecan is a substrate for both ABCB1 (P-glycoprotein) and ABCG2 (BCRP). Inhibitors of ABCB1 and ABCG2 administered with oral topotecan have been shown to increase topotecan exposure.

Cyclosporin A (an inhibitor of ABCB1, ABCC1 [MRP-1], and CYP3A4) administered with oral topotecan increased topotecan AUC to approximately 2 - 2.5-fold of control.

Patients should be carefully monitored for adverse reactions when oral topotecan is administered with a substance known to inhibit ABCB1 or ABCG2 (see section 5.2).

When combining topotecan with other chemotherapy agents, reduction of the doses of each medicinal product may be required to improve tolerability. However, when 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. Currently there is only limited experience in combining oral topotecan with other chemotherapy agents.

The pharmacokinetics of topotecan were generally unchanged when co-administered with ranitidine.

4.6 Fertility, pregnancy and lactation

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

As with all cytotoxic chemotherapy, patients being treated with topotecan must be advised that they or their partner must use an effective method of contraception.

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.

Breast-feeding
Topotecan is contraindicated 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 of 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 clinical studies involving patients with relapsed small cell lung cancer, the dose-limiting toxicity of oral topotecan monotherapy was found to be haematological. Toxicity was predictable and reversible. There were no signs of cumulative haematological or non-haematological toxicity.

The frequencies associated with the haematological and non-haematological adverse events presented are for adverse events considered to be related/possibly related to oral topotecan therapy.

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), and not known (cannot be estimated from the available data).

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

Infections and infestations	
Very common	Infection
Common	Sepsis[1]
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)
Immune system disorders	
Common	Hypersensitivity reaction including rash
Rare	Anaphylactic reaction, angioedema, urticaria
Metabolism and nutrition disorders	
Very common	Anorexia (which may be severe)
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), which may lead to dehydration (see sections 4.2 and 4.4)
Common	Abdominal pain[2], constipation, mucositis, dyspepsia
Not known	Gastrointestinal perforation
Hepatobiliary disorders	
Common	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Very common	Alopecia
Common	Pruritus
General disorders and administration site conditions	
Very common	Fatigue
Common	Asthenia, pyrexia, malaise
Not known	Mucosal inflammation
[1] Fatalities due to sepsis have been reported in patients treated with topotecan (see section 4.4). [2] Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see section 4.4)	

The 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).

Safety data are presented based on an integrated data set of 682 patients with relapsed lung cancer administered 2,536 courses of oral topotecan monotherapy (275 patients with relapsed SCLC and 407 with relapsed non-SCLC).

Haematological

Neutropenia
Severe neutropenia (Grade 4 - neutrophil count < 0.5 x 10^9/l) occurred in 32 % of patients in 13 % of courses. Median time to onset of severe neutropenia was day 12 with a median duration of 7 days. In 34 % of courses with severe neutropenia, the duration was > 7 days. In course 1 the incidence was 20 %, by course 4 the incidence was 8 %. Infection, sepsis and febrile neutropenia occurred in 17 %, 2 %, and 4 % of patients, respectively. Death due to sepsis occurred in 1 % of patients. Pancytopenia has been reported. Growth factors were administered to 19 % of patients in 8 % of courses.

Thrombocytopenia
Severe thrombocytopenia (Grade 4 - platelets <10 x 10^9/l) occurred in 6 % of patients in 2 % of courses. Median time to onset of severe thrombocytopenia was day 15 with a median duration of 2.5 days. In 18 % of courses with severe thrombocytopenia the duration was > 7 days. Moderate thrombocytopenia (Grade 3 - platelets between 10.0 and 50.0 x 10^9/l) occurred in 29 % of patients in 14 % of courses. Platelet transfusions were given to 10 % of patients in 4 % of courses. Reports of significant sequelae associated with thrombocytopenia including fatalities due to tumour bleeds have been infrequent.

Anaemia
Moderate to severe anaemia (Grade 3 and 4 – Hb ≤ 8.0 g/dl) occurred in 25 % of patients (12 % of courses). Median time to onset of moderate to severe anaemia was day 12 with a median duration of 7 days. In 46 % of courses with moderate to severe anaemia, the duration was > 7 days. Red blood cell transfusions were given in 30 % of patients (13 % of courses). Erythropoietin was administered to 10 % of patients in 8 % of courses.

Non-haematological
The most frequently reported non-haematological effects were nausea (37 %), diarrhoea (29 %), fatigue (26 %), vomiting (24 %), alopecia (21 %) and anorexia (18 %). All cases were irrespective of associated causality. For severe cases (CTC Grade 3/4) reported as related / possibly related to topotecan administration the incidence was diarrhoea 5 % (see section 4.4), fatigue 4 %, vomiting 3 %, nausea 3 % and anorexia 2 %.

The overall incidence of drug-related diarrhoea was 22 %, including 4 % with Grade 3 and 0.4 % with Grade 4. Drug-related diarrhoea was more frequent in patients ≥65 years of age (28 %) compared to those less than 65 years of age (19 %).

Complete alopecia related/possibly related to topotecan administration was observed in 9 % of patients and partial alopecia related/possibly related to topotecan administration in 11 % of patients.

Therapeutic interventions associated with non-haematological effects included anti-emetic agents, given to 47 % of patients in 38 % of courses and anti-diarrhoeal agents, given to 15 % of patients in 6 % of courses. A 5-HT3 antagonist was administered to 30 % of patients in 24 % of courses. Loperamide was administered to 13 % of patients in 5 % of courses. The median time to onset of Grade 2 or worse diarrhoea was 9 days.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il.

4.9 Overdose

Overdoses have been reported in patients being treated with topotecan capsules (up to 5 fold of the recommended dose) and intravenous topotecan (up to 10 fold of the recommended dose). The signs and symptoms observed following overdose were consistent with the known undesirable events associated with topotecan (see section 4.8). The primary complications of overdose are bone marrow suppression and mucositis. In addition, elevated hepatic enzymes have been reported with intravenous topotecan overdose.
There is no known antidote for topotecan overdose. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 **Pharmacodynamic properties**

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

Mechanism of action

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.

Clinical efficacy and safety

Relapsed SCLC
A Phase III study (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 plus BSC, 90 days for BSC alone) and for whom re-treatment with intravenous chemotherapy was not considered appropriate. In the oral topotecan plus BSC group there was a statistically significant improvement in overall survival compared with the BSC alone group (Log-rank p=0.0104). The unadjusted hazard ratio for the oral topotecan plus BSC group relative to the BSC alone group was 0.64 (95 % CI: 0.45, 0.90). Median survival in patients treated with oral topotecan plus 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 plus BSC.

One Phase II study (Study 065) and one Phase III 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 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.

Paediatric population
The safety and effectiveness of oral topotecan in paediatric patients have not been established.

5.2 Pharmacokinetic properties

Distribution

The pharmacokinetics of topotecan after oral administration have been evaluated in cancer patients following doses of 1.2 to 3.1 mg/m^2/day and 4 mg/m^2/day administered daily for 5 days. The bioavailability of oral topotecan (total and lactone) in humans is approximately 40 %. Plasma concentrations of total topotecan (i.e. lactone and carboxylate forms) and topotecan lactone (active moiety) peak at approximately 2.0 hours and 1.5 hours, respectively, and decline bi-exponentially with mean terminal half-life of approximately 3.0 to 6.0 hours. Total exposure (AUC) increases approximately proportionally with dose. There is little or no accumulation of topotecan with repeated daily dosing and there is no evidence of a change in pharmacokinetics after multiple doses. Preclinical studies indicate plasma protein binding of topotecan is low (35 %) and distribution between blood cells and plasma was fairly homogeneous.

Biotransformation
A major route of clearance of topotecan is by hydrolysis of the lactone ring to form the ring-opened carboxylate. Other than hydrolysis, topotecan is cleared predominantly renally, with a minor component metabolised to the N-desmethyl metabolite (SB-209780) identified in plasma, urine and faeces.

Elimination

Overall recovery of topotecan-related material following five daily doses of topotecan was 49 to 72 % (mean 57 %) of the administered oral dose. Approximately 20 % was excreted as total topotecan and 2 % was excreted as N-desmethyl topotecan in the urine. Faecal elimination of total topotecan accounted for 33 % while faecal elimination of N-desmethyl topotecan was 1.5 %. Overall, the N-desmethyl metabolite contributed a mean of less than 6 % (range 4-8 %) of the total topotecan related material accounted for in the urine and faeces. O-glucuronides of both topotecan and N-desmethyl topotecan have been identified in the urine. The mean metabolite: parent plasma AUC ratio was less than 10 % for both total topotecan and topotecan lactone.

In vitro, topotecan did not inhibit human P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19,

CYP2D6, CYP2E, CYP3A or CYP4A, nor did it inhibit the human cytosolic enzymes dihydropyrimidine or xanthine oxidase.

Following co-administration of the ABCB1 (P-gp) and ABCG2 (BCRP) inhibitor, elacridar (GF120918) at 100 to 1,000 mg with oral topotecan, the $AUC_{0-\infty}$ of topotecan lactone and total topotecan increased approximately 2.5-fold (see section 4.5 for guidance).

Administration of oral cyclosporine A (15 mg/kg), an inhibitor of transporters ABCB1 (P-gp) and ABCC1 (MRP-1) as well as the metabolising enzyme CYP3A4, within 4 hours of oral topotecan increased the dose normalised AUC0-24h of topotecan lactone and total topotecan approximately 2.0- and 2.5-fold, respectively (see section 4.5).

The extent of exposure was similar following a high-fat meal and in the fasted state, while t_{max} was delayed from 1.5 to 3 hours (topotecan lactone) and from 3 to 4 hours (total topotecan).

Special populations

Hepatic impairment

The pharmacokinetics of oral topotecan have not been studied in patients with hepatic impairment (see section 4.2 and 4.4).

Renal impairment

Results of a cross-study analysis suggest that the exposure to topotecan lactone, the active moiety following topotecan administration, increases with decreased renal function. Geometric mean topotecan lactone dose-normalised $AUC_{(0-\infty)}$ values were 9.4, 11.1 and 12.0 ng*h/ml in subjects with creatinine clearance values of more than 80 ml/min, 50 to 80 ml/min and 30 to 49 ml/min, respectively. In this analysis, creatinine clearance was calculated using the Cockcroft-Gault method. Similar results were obtained if glomerular filtration rate (ml/min) was estimated using the MDRD formula corrected for body weight. Patients with creatinine clearance >60 ml/min have been included in efficacy/safety studies of topotecan. Therefore, use of the normal starting dose in patients with a mild decrease in renal function is considered established (see section 4.2).

Korean patients with renal impairment had generally higher exposure than non-Asian patients with the same degree of renal impairment. The clinical significance of this finding is unclear. Geometric mean topotecan lactone dose-normalised $AUC_{(0-\infty)}$ values for Korean patients were 7.9, 12.9 and 19.7 ng*h/ml in subjects with creatinine clearance values of more than 80 ml/min, 50 to 80 ml/min and 30 to 49 ml/min, respectively (see section 4.2 and 4.4). There are no data from Asian patients with renal impairment other than Koreans.

Gender
A cross-study analysis in 217 patients with advanced solid tumours indicated that gender did not affect the pharmacokinetics of HYCAMTIN capsules to a clinically relevant extent.

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

HYCAMTIN 0.25 mg hard gelatin capsules

Capsule contents:
Hydrogenated vegetable oil
Glyceryl monostearate

Capsule shell:
Gelatin
Titanium dioxide (E171)

Sealing band:
Gelatin

Black ink:
Black iron oxide (E172)
Shellac
Ethanol Anhydrous
Propylene glycol
Isopropyl alcohol
Butanol
Ammonia Solution concentrated
Potassium hydroxide

HYCAMTIN 1 mg hard gelatin capsules

Capsule contents
Hydrogenated vegetable oil
Glyceryl monostearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)

Sealing band
Gelatin

Black ink
Black iron oxide (E172)
Shellac
Ethanol Anhydrous
Propylene glycol
Isopropyl alcohol
Butanol
Ammonia Solution concentrated
Potassium hydroxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC).

Keep in the original package in order to protect from light.

Do not freeze.

6.5 Nature and contents of container

White opaque PVC / PCTFE (polyvinyl chloride/ polychlorotrifluoroethylene thermoform blister sealed with Aluminium / Polyethylenterephtalate (PET) / paper foil lidding.

Each pack contains 10 capsules.

6.6 Special precautions for disposal and other handling

HYCAMTIN capsules should not be opened or crushed.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Registration Holder and Importer and it's address

Novartis Israel Ltd., P.O.B: 7126, Tel-Aviv

8. Registration Number

HYCAMTIN 0.25 mg: 141 37 31862
HYCAMTIN 1 mg: 141 38 31863

Revised in Dec 2020.