Pharmacokinetics of oral topotecan have been evaluated in cancer patients following doses of 1.2 to 3.1 mg/m² and 4 mg/dose administered daily for 5 days.

Absorption
Topotecan is rapidly absorbed with peak plasma concentrations occurring between 1 to 2 hours following oral administration.

Distribution
The binding of topotecan to plasma proteins was low (35%) and its distribution between blood cells and plasma was homogeneous.

Metabolism
A major route of inactivation of topotecan is a reversible pH-dependent ring opening to the inactive carboxylate form. Metabolism accounts for less than 10% of the elimination of topotecan. An N-desmethyl metabolite was found in urine, plasma, and faeces. Following oral administration the mean metabolite: parent AUC ratio was less than 10% for both total topotecan and topotecan lactone. An O-glucuronide of topotecan and N-desmethyl topotecan has been identified in the urine.

Elimination
Following oral administration, the plasma concentrations decline bi-exponentially. The pharmacokinetics of oral topotecan are approximately dose proportional. There is little or no accumulation of either formulation of topotecan with repeated daily dosing, and there is no evidence of a change in the pharmacokinetics with multiple dosing.

Pharmacodynamics
The pharmacokinetics of topotecan after oral administration have been evaluated in cancer patients following doses of 1.2 to 3.1 mg/m² and 4 mg/dose administered daily for 5 days.
therapy: was 84 days for oral topotecan + BSC, and 90 days for BSC. Oral topotecan plus BSC group had a statistically significant and clinically meaningful improvement in overall survival compared with the BSC alone group in the (ITT) population (Log-rank p=0.0104). The median survival for patients treated with oral topotecan + BSC was 25.9 weeks [95% confidence interval (C.I.) 18.3, 31.6] compared to 13.9 weeks [95% C.I. 11.1, 16.6] for patients receiving BSC alone. The unadjusted hazard ratio for oral topotecan plus BSC relative to BSC alone was 0.64 (95% CI: 0.45, 0.90). In study 478, 58% of subjects in oral topotecan plus BSC arm and 51% of patients in BSC only arm constituted the sub-group of subjects having refractory disease (time to progression 45–90 days from end of 1st line chemotherapy). Both refractory disease subjects and sensitive disease subjects showed a consistent survival benefit for oral topotecan plus BSC arm relative to BSC only arm (Hazard ratio (95% CI): 0.62 (0.39, 0.98) for refractory disease subjects, 0.65 (0.39, 1.01) for sensitive disease subjects).

Odds ratios (OR) for symptom benefit (improvement) using a Generalised Estimating Equations (GEE) model analysis of patients’ self-reports on the Patient Symptom Assessment in Lung Cancer (PSALC) scale showed a consistent trend towards symptom benefit with oral topotecan plus BSC alone across all of the 9 lung cancer symptoms assessed. In addition, a significant symptom benefit for shortness of breath (OR=2.18: 95% CI: 1.09, 4.38), interference with sleep (OR=2.16: 95% CI: 1.15, 4.06) and fatigue (OR=2.29: 95% CI: 1.25, 4.19) was observed.

Patient self-reports on a lung cancer symptom scale (Patient Symptom Assessment in Lung Cancer) showed a consistent trend for symptom benefit for oral topotecan+BSC over BSC alone across all 9 symptoms, with a statistically significant benefit for shortness of breath, interference with sleep, and fatigue. EuroQoL EQ-5D results showed that oral topotecan +BSC was associated with a statistically significant slower worsening of health status compared to BSC alone. One Phase II study (Study 065) and one Phase III study (Study 396) were conducted to evaluate the efficacy of oral topotecan (2.3 mg/m²/day for 5 days, every 21 days) versus i.v.topotecan (1.5 mg/m²/day for 5 days every 21 days) in patients who had relapsed ≥ 90 days after completion of one prior regimen of chemotherapy. Median survival in the oral topotecan arms were not different from the median survival in the i.v. topotecan arms in Studies 065 and 396, respectively, although the hazard ratio in each study trended in favour of oral topotecan (see Table 1). Neither the response rate nor the median time to progression were different between the arms in either study.

### Table 1. Summary of Survival, Response Rate, and Time to Progression in SCLC Patients Treated with Oral Hycamtin or IV Hycamtin

<table>
<thead>
<tr>
<th></th>
<th>Study 065</th>
<th>Study 396</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral topotecan</td>
<td>IV topotecan</td>
</tr>
<tr>
<td></td>
<td>(N = 52)</td>
<td>(N = 54)</td>
</tr>
<tr>
<td><strong>Median survival (weeks)</strong></td>
<td>32.3</td>
<td>25.1</td>
</tr>
<tr>
<td></td>
<td>(26.3, 40.9)</td>
<td>(21.1, 33.0)</td>
</tr>
<tr>
<td><strong>Hazard ratio (95% CI)</strong></td>
<td>0.88 (0.59, 1.31)</td>
<td>0.88 (0.7, 1.11)</td>
</tr>
<tr>
<td><strong>Response rate (%)</strong></td>
<td>23.1</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td>(11.6, 34.5)</td>
<td>(5.3, 24.3)</td>
</tr>
<tr>
<td><strong>Difference in response rate (95% CI)</strong></td>
<td>-6.6, 23.1</td>
<td>-12.6, 5.5</td>
</tr>
<tr>
<td><strong>Median time to progression (weeks)</strong></td>
<td>14.9</td>
<td>13.1</td>
</tr>
<tr>
<td></td>
<td>(8.3, 21.3)</td>
<td>(11.6, 18.3)</td>
</tr>
<tr>
<td><strong>Hazard ratio (95% CI)</strong></td>
<td>0.90 (0.60, 1.35)</td>
<td>1.21 (0.96, 1.53)</td>
</tr>
</tbody>
</table>

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

### Integrated safety data

Safety data is presented on an integrated data set of 682 patients with relapsed lung cancer administered 2536 courses of oral topotecan monotherapy (275 patients with relapsed SCLC and 407 with relapsed non-SCLC) (see Adverse Reactions).

### Haematological

Neutropenia: Severe neutropenia (Grade 4 - neutrophil count less than 0.5 x 10⁹/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 greater than 7 days. In course 1 the incidence was 20%, by course 4 the incidence was 8%. Infection, sepsis and febrile neutropenia occurred in 17%, 12%, and 7% of patients respectively.

Death due to sepsis occurred in 1% of patients. Growth factors were administered to 19% of patients in 8% of courses.

Thrombocytopenia: Severe thrombocytopenia (Grade 4 - platelets less than 10 x 10⁹/L (as defined by v2 of CTC criteria)) occurred in 6% of patients in 2% of courses. Median time to onset of severe thrombocytopenia was Day 15 with a median duration of 5.5 days. In 18% of courses with severe thrombocytopenia the duration was greater than 7 days. Moderate thrombocytopenia (Grade 3 - platelets between greater than or equal to 10.0 and less than 50.0 x 10⁹/L) occurred in 25% of patients in 14% of courses. Platelet transfusions were given to 10% of patients in 4% of courses.

### Non-haematological

The most frequently reported non-haematological adverse reactions, all cases irrespective of associated causality were nausea (37%), diarrhoea (29%), fatigue (26%), vomiting (24%), alopecia (21%) and anorexia (18%). For severe cases (CTC grade 3/4) reported as related / possibly related to topotecan administration the incidence was diarrhoea 5%, fatigue 4%, vomiting 3%, nausea 3% and anorexia 2%. This content is from a study comparing oral topotecan to intravenous topotecan in patients with relapsed small cell lung cancer, evaluating survival, response rate, and symptom benefit, and reporting on the incidence and duration of haematological and non-haematological adverse events.
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 greater than or equal to 65 years of age (28%) compared to those less than 65 years of age (19%). 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.

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.

Pre-clinical Safety Data

Carcinogenesis, mutagenesis

The carcinogenic potential of topotecan has not been studied. In common with a number of other cytotoxic agents, and 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.

Reproductive toxicology

As with other cytotoxics, topotecan was also shown to cause embryo-foetal toxicity when given to rats (0.59 mg/m²/day) and rabbits (1.25 mg/m²/day) at doses less than the clinical i.v. dose in humans (1.5 mg/m²/day). A dose of 0.59 mg/m² was teratogenic in rats (predominantly effects of the eye, brain, skull and vertebrae).

INDICATIONS

- Indicated for the treatment of patients with relapsed small cell lung carcinoma.

For efficacy data see Clinical Studies

DOSAGE AND ADMINISTRATION

Prior to administration of the first course of Topotecan (Hycamtin®), patients must have a baseline neutrophil count of more than or equal to 1.5 x 10⁹/L, a platelet count of more than or equal to 100 x 10⁹/L and a haemoglobin level of more than or equal to 9g/dL (after transfusion if necessary).

Initial dose

The recommended dose of oral Topotecan (Hycamtin®) is 2.3 mg/m² daily for five consecutive days every 21 days. The hard capsule(s) must be swallowed whole, and must not be chewed, crushed or divided.

oral Topotecan (Hycamtin®) may be taken with or without food.

Subsequent doses

For patients who experience Grade 3 or 4 diarrhoea, the oral Topotecan (Hycamtin®) dose should be reduced by 0.4 mg/m²/day for subsequent courses (see Warnings and Precautions). Patients with Grade 2 diarrhoea may need to follow the same dose modification guidelines.

Topotecan (Hycamtin®) should not be re-administered unless the neutrophil count is more than or equal to 1 x 10⁹/L, the platelet count is more than or equal to 100 x 10⁹/L, and the haemoglobin level is more than or equal to 9g/dL (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer Topotecan (Hycamtin®) with other medications (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 or equal to 0.5 x 10⁹/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/m²/day to 1.9 mg/m²/day (or subsequently down to 1.5 mg/m²/day if necessary).

Doses should be similarly reduced if the platelet count falls below 25 x 10⁹/L. In clinical trials, oral Topotecan (Hycamtin®) was discontinued if the dose had to be reduced below 1.5 mg/m².

Populations

Children

Due to limited data on efficacy and safety in the paediatric population, no recommendation for treatment of children with Topotecan (Hycamtin®) can be given.

Elderly

No overall differences in effectiveness were observed between patients over 65 years and younger adult patients. However, it has been reported that patients older than 65 years old receiving oral topotecan experienced an increase in drug related diarrhoea compared to those younger than 65 years of age (see Warnings and Precautions and Adverse Reactions).

Renal impairment

Dosing recommendations for patients receiving oral topotecan with a creatinine clearance less than 60 mL/min have not been established.

Hepatic impairment

Pharmacokinetics of oral Topotecan (Hycamtin®) has not been specifically studied in patients with impaired hepatic function.

Contraindications

Topotecan (Hycamtin®) is contraindicated in patients who

- have a history of severe hypersensitivity reactions to topotecan and/or its excipients
- are pregnant or breast-feeding
- already have severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils less than 1.5 x 10⁹/L and/or a platelet count of less than 100 x 10⁹/L.

Warnings and Precautions

Topotecan (Hycamtin®) should be initiated under the direction of a physician experienced in the use of cytotoxic agents.
Haematological toxicity is dose-related and full blood count including platelets should be monitored regularly (see Dosage and Administration).

As with other cytotoxic drugs, Topotecan (Hycamtin®) can cause severe myelosuppression. Myelosuppression leading to sepsis and fatalities due to sepsis have been reported in patients treated with topotecan (see Adverse Reactions). 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.

Topotecan has been associated with reports of interstitial lung disease (ILD), some of which have been fatal (see Adverse Reactions). Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation and use of pneumotoxic drugs 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 (Hycamtin®) should be discontinued if a new diagnosis of ILD is confirmed.

Dose adjustment may be necessary if Topotecan (Hycamtin®) is administered in combination with other cytotoxic agents (see Interactions).

Diarrhoea, including severe diarrhoea requiring hospitalisation, has been reported during treatment with oral topotecan. The incidence of diarrhoea has been reported to be greater in patients receiving oral topotecan compared to those receiving topotecan i.v. Additionally, in patients with relapsing small cell lung cancer, greater than 65 years of age, there is substantially higher risk of severe diarrhoea and subsequent hospitalisation than in patients less than 65 years of age. Communication with patients prior to drug administration regarding diarrhoea and proactive management of all signs of diarrhoea is important. Physicians are advised to follow guidelines that describe the aggressive management of this event. This includes use of anti-diarrhoeal agents, administration of fluids and electrolytes and interruption or discontinuation of therapy with oral topotecan. Diarrhoea related to oral topotecan can occur at the same time as drug-related neutropenia and its sequelae (see Dosage and Administration).

**Effects on Ability to Drive and Use Machines**

Caution should be observed when driving or operating machinery if fatigue and asthenia persist.

**DRUG INTERACTIONS**

As with other myelosuppressive cytotoxic agents, greater myelosuppression is likely to be seen when Topotecan (Hycamtin®) is used in combination with other cytotoxic agents (e.g. paclitaxel or etoposide) thereby necessitating dose reduction. However, in combining with platinum agents (e.g. cisplatin or carboplatin), there is a distinct sequence-dependent interaction depending on whether the platinum agent is given on day 1 or 5 of the topotecan dosing.

**When oral Topotecan (Hycamtin®) was combined with cisplatin in a randomized Phase 3 study in chemotherapy-naive, extensive disease, small cell lung cancer patients, the regimen of oral Topotecan (Hycamtin®) (1.7 mg/m² for 5 days) with IV cisplatin (80 mg/m² on day 5) was selected.**

**Topotecan does not inhibit human cytochrome P450 enzymes (see Pharmacokinetics).**

Topotecan is a substrate for both ABCG2 (BCRP) and ABCB1 (P-glycoprotein). Inhibitors of ABCB1 and ABCG2 (e.g. elacridar) administered with oral topotecan increased topotecan exposure (see Pharmacokinetics - Absorption).

Cyclosporin A (an inhibitor of ABCB1, ABCC1 [MRP-1], and CYP3A4) with oral topotecan increased topotecan AUC (see Pharmacokinetics - Absorption).

Patients should be carefully monitored for adverse events when oral topotecan is administered with a drug known to inhibit ABCG2 or ABCB1 (see Pharmacokinetics - Absorption).

The pharmacokinetics of topotecan were generally unchanged when coadministered with ranitidine.

**PREGNANCY AND LACTATION**

Topotecan has been shown to be both embryotoxic and foetotoxic in preclinical studies. As with other cytotoxic drugs, topotecan may cause foetal harm when administered to pregnant women and therefore is contraindicated during pregnancy. Women should be advised to avoid becoming pregnant during therapy with topotecan and to inform the treating physician immediately should this occur.

Topotecan (Hycamtin®) is contraindicated during breast-feeding.

**ADVERSE EFFECTS**

No evidence of significant cardiotoxicity, neurotoxicity or major organ toxicity has been observed with topotecan. Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (greater than or equal to 1/10), common (greater than or equal to 1/100 and less than 1/10), uncommon (greater than or equal to 1/1000 and less than 1/100), rare (greater than or equal to 1/10,000 and less than 1/1000) and very rare (less than 1/10,000) including isolated reports, not known (cannot be estimated from the available data). Very common, common and uncommon events were generally determined from clinical trial data.

The following frequencies are estimated at the standard recommended doses of topotecan according to indication and formulation.

Further information regarding incidence and grade of toxicity is presented in the Clinical Studies section.

**Infections and infestations**

- Very common: Infection
- Common: Sepsis (see Warnings and Precautions)

**Blood and lymphatic system disorders**

- Very Common: Anaemia, febrile neutropenia, leucopenia, neutropenia (see Gastrointestinal disorders), thrombocytopenia
- Common: Pancytopenia
- Not known: Severe bleeding (associated with thrombocytopenia)
Immune system disorders
Common Hypersensitivity, including rash

Metabolism and nutrition disorders
Very Common Anorexia (which may be severe)

Respiratory, thoracic and mediastinal disorders
Rare Interstitial lung disease

Gastrointestinal disorders
Very Common Diarrhoea (see Warnings and Precautions), nausea and vomiting (all of which may be severe), abdominal pain*, constipation and stomatitis.

*With oral topotecan the overall incidence of drug-related diarrhoea was 22%, including 4% with Grade 3 and 0.4% with Grade 4. With oral topotecan, drug-related diarrhoea was more frequent in patients greater than or equal to 65 years of age (28%) compared to those less than 65 years of age (19%). After i.v. topotecan, drug-related diarrhoea in patients greater than 65 years of age was 10%.

Hepatobiliary disorders
Common Hyperbilirubinaemia

Skin and subcutaneous disorders
Very Common Alopecia

General disorders and administrative site conditions
Very Common Asthenia, fatigue, pyrexia
Common Malaise

OVERDOSAGE AND TREATMENT
Symptoms and Signs
The primary complications of overdosage are anticipated to be bone marrow suppression and stomatitis.

Treatment
There is no known antidote for Topotecan (Hycamtin®) overdosage.

STORAGE CONDITIONS
Store between 2-8°C. Protect from light.

INSTRUCTIONS FOR USE/HANDLING
Topotecan (Hycamtin®) capsules must not be opened or crushed. If the capsules are punctured or leaking, you should immediately wash your hands thoroughly with soap and water. If you get it in your eyes, wash them immediately with gently flowing water for at least 15 minutes. Consult your doctor/healthcare provider after eye contact or if you experience a skin reaction.

AVAILABILITY
Topotecan (Hycamtin®) 0.25mg capsule: Box of 10’s
Topotecan (Hycamtin®) 1mg capsule: Box of 10’s

CAUTION
Foods, Drugs Devices and Cosmetics Act prohibits dispensing without prescription. Keep all medicines out of reach of children.

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GlaxoSmithKline Philippines Inc.
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Tel no. 892-0761

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