癌康定膠囊 0.25 毫克 /1 毫克
HYCAMTIN® Capsules 0.25 mg, 1 mg

0.25 mg 衛署藥輸字第 025244 號
1 mg 衛署藥輸字第 025245 號

警告：可能導致骨髓抑制
HYCAMTIN 可能會導致嚴重的骨髓抑制。僅能用於基礎嗜中性白血球計數 ≥1,500 cells/mm³ 且血小板計數 ≥100,000 cells/mm³ 之患者。應監測血球細胞計數。

【適應症】
復發性小細胞肺癌。

【劑量與用法】
本藥須由醫師處方使用。

【建議劑量】
HYCAMTIN 膠囊之建議劑量為 2.3 mg/m²/day，每日口服一次，每個療程連續五天，每 21 天重覆此療程一次。計算劑量至最接近 0.25 mg，且應開立最少數量之 1 mg 及 0.25 mg 膠囊。五天皆應處方相同數量之膠囊。
HYCAMTIN 膠囊可與食物或單獨服用。膠囊應整粒吞服，不可咀嚼、壓碎或打開膠囊服用。不可因噁吐吐出藥物而開一個替代劑量。
腹瀉：
不可對仍在第 3 級或 4 級腹瀉的患者投予 HYCAMTIN 膠囊。在恢復至第 1 級（含）以下之後，後續的療程應將 HYCAMTIN 的劑量減少 0.4 mg/m²/day（參見警語及注意事項）。

【劑量調整準則】
血液學毒性：
在嗜中性白血球回復至高於 1,000 cells/mm³，血小板回復至高於 100,000 cells/mm³，血紅素濃度回復至高於或等於 9.0 g/dL（必要時可輸血）之前，切勿在後續療程投予 HYCAMTIN 膠囊。
- 在下列情況下，應將 HYCAMTIN 膠囊的劑量減少 0.4 mg/m²/day：
  - 嗜中性白血球計數低於 500 cells/mm³，併有發燒或感染或持續 7 天以上；
  - 嗜中性白血球計數為 500 至 1,000 cells/mm³ 持續超過療程的第 21 天；
  - 血小板計數低於 25,000 cells/mm³。

腎功能不全：
HYCAMTIN 膠囊用於中度及重度腎功能損傷之患者的建議起始劑量如下：

表 1　腎功能不全患者的劑量降低準則

腎功能不全程度	肌酸酐廓清率[a] (mL/min)	劑量 (mg/m²/day)
中度	30-49	1.5[b]
重度	<30	0.6[b]

[a] 採用理想體重的 Cockroft-Gault 公式計算而得。
[b] 在第一個療程之後，如果未出現任何嚴重的血液學或胃腸道毒性反應，可將劑量提高 0.4 mg/m²/day。

【劑型及劑量】
HYCAMTIN 膠囊內含 topotecan hydrochloride，其含量是以 topotecan 游離鹼基標示。0.25 毫克膠囊為不透明白色到黃白色，印有 HYCAMTIN 及 0.25 mg 字樣。
1 毫克膠囊為不透明粉紅色，印有 HYCAMTIN 及 1 mg 字樣。

【禁忌症】
HYCAMTIN 禁用於對 topotecan 有嚴重過敏反應病史的患者。

【警語及注意事項】

【骨髓抑制】
骨髓抑制（主要為嗜中性白血球減少症）為 HYCAMTIN 的一種劑量限制毒性 (dose-limiting toxicity)。嗜中性白血球減少症不會隨時間累積。下列骨髓抑制資料，來自每天使用 2.3 mg/m²/day HYCAMTIN 膠囊，連續治療 5 天之 4 項胸腔惡性腫瘤試驗 (N = 682) 的整合安全性資料庫。嗜中性白血球及血小板平均於第 15 日降至最低點。
嗜中性白血球減少症：32% 之患者產生第 4 級嗜中性白血球減少症 (<500 cells/mm³)，病程中位數為七日，且最常於第 1 個療程中發生 (20% 的患者)。嗜中性白血球減少症的臨床後遺症包括感染 (17%)、發熱性嗜中性白血球減少症 (4%)、敗血症 (2%) 以及因敗血症而導致死亡 (1%)。曾接獲全血球減少症之報告。
Topotecan 可能會造成致死性闌尾炎（小腸結腸炎）。如患者有發燒、嗜中性白血球減少症及腹痛情況，應考慮是否可能發生闌尾炎（參參剛量與用法）。
血小板減少症：6% 之患者產生第 4 級血小板減少症 (<10,000 cells/mm³)，病程中位數為三日。
貧血：25% 之患者產生第 3 或 4 級貧血症 (<8 g/dL)。
對嗜中性白血球計數 ≥ 1,500 cells/mm³ 及血小板計數 ≥ 100,000 cells/mm³ 的患者，才可投予第一療程的 HYCAMTIN。使用 HYCAMTIN 治療時，應頻繁的監測周邊血球數量。關於出現血液學毒性時的後續療程，應參見劑量調整準則（請參見劑量與用法）。

【腹瀉】
使用 HYCAMTIN 膠囊治療期間可能會發生腹瀉，包含需住院治療之嚴重且危及生命的腹瀉。HYCAMTIN 膠囊所引起的腹瀉，可能會與藥物相關嗜中性白血球減少症及其後遺症同時發生。在 4 項的肺癌試驗中接受 HYCAMTIN 膠囊治療的 682 位患者中，HYCAMTIN 膠囊所引起之腹瀉的發生率為 22%，其中有 4% 屬於第 3 級，有 0.4% 屬於第 4 級。在接受 HYCAMTIN 膠囊治療的試驗組中，第 3 或 4 級腹瀉的發生率（5 天內）為 5%，和第 3 或 4 級嗜中性球白血球減少事件的發生率相近。在接受 HYCAMTIN 膠囊治療的試驗組中，開始出現第 2 級（含）以上之腹瀉的中位時間為 9 天。應積極處理 HYCAMTIN 膠囊所引起的腹瀉。不可對發生第 3 或 4 級腹瀉的患者投予 HYCAMTIN 膠囊。在恢復至第 1 級（含）以下之後，應降低 HYCAMTIN 的劑量（參見劑量與用法）。

【間質性肺病】
曾有在使用 HYCAMTIN 期間發生間質性肺病 (ILD) 的病例，包括死亡病例。潛在的危險因子包括 ILD 病史、肺纖維變性、肺癌、胸腔放射治療以及使用肺毒性藥物及 / 或細胞集落刺激因子。應監視患者是否出現發生間質性肺病的肺部症狀（如咳嗽、發燒、呼吸困難及 / 或缺氧），如果確定發生新的 ILD，則應停用 HYCAMTIN。

【胚胎胎兒毒性】
HYCAMTIN 用於懷孕婦女時，可能會導致胎兒受到傷害。對大鼠和兔子在器官形成期間投予 topotecan 會造成胚胎死亡、胎兒毒性和畸胎。若懷孕期間使用本藥物，或患者於用藥期間懷孕，應向患者詳述胎兒可能發生的危險（參見特殊使用族群）。
應囑咐具有生育能力的女性患者，在使用 HYCAMTIN 治療期間應採取有效的避孕措施，且在使用最後一劑 HYCAMTIN 之後亦應繼續避孕至少 1 個月。應囑咐患者，如果她們在使用 HYCAMTIN 期間懷孕或疑似懷孕，一定要和他們的健康照護人員聯繫（參見特殊使用族群）。

【不良反應】
下列嚴重不良反應在下文及本仿單的其他段落有詳細的說明：
- 骨髓抑制（參見警語及注意事項）
- 腹瀉（參見警語及注意事項）
- 間質性肺病（參見警語及注意事項）

【臨床試驗經驗】
由於臨床試驗進行的條件差異很大，臨床試驗中觀察到的特定藥物不良反應發生率，不能與另一種藥物在臨床試驗中的不良反應發生率直接比較，也未必能反映實際臨床業務所觀察到之發生率。
曾針對 682 位接受過至少一劑 HYCAMTIN 膠囊的肺癌患者（三項復發性小細胞肺癌 [SCLC] 試驗與一項復發性非小細胞肺癌 [NSCLC] 試驗）評估 HYCAMTIN 膠囊的安全性。四項試驗中的患者都患有晚期肺癌惡性腫瘤，且先前都曾接受化學治療做為第一線治療。HYCAMTIN 膠囊的給藥方式為每 21 天連續 5 天投予 2.3 mg/m²/day 的劑量。這四項試驗的中位療程數為 3 個療程（範圍：1 至 20 個療程）。
表 2 說明使用 HYCAMTIN 膠囊治療的復發性 SCLC 患者及整體肺癌患者族群的血液學及非血液學不良反應。

表 2　在四項肺癌試驗中，接受 HYCAMTIN 膠囊加上最佳支持照護 (BSC) 治療之小細胞肺癌患者不良反應發生率 (≥5%)

不良反應	HYCAMTIN 膠囊 + BSC (N = 70)			HYCAMTIN 膠囊 肺癌患者族群 (N = 682)		
	所有等級 (%)	第 3 級 (%)	第 4 級 (%)	所有等級 (%)	第 3 級 (%)	第 4 級 (%)
血液學						
貧血	94	15	10	98	18	7
嗜中性白血球減少症	91	28	33	83	24	32
血小板減少症	81	30	7	81	29	6
非血液學						
噁心	27	1	0	33	3	0
腹瀉	14	4	1	22	4	0.4
嘔吐	19	1	0	21	3	0.4
禿頭症	10	0	0	20	0.1	0
疲勞	11	0	0	19	4	0.1
厭食症	7	0	0	14	2	0
無力	3	0	0	7	2	0
發燒	7	1	0	5	1	1

BSC = 最佳支持照護
N = 接受治療患者之總數
不良反應依據 NCI Common Toxicity Criteria 第 2.0 版分級評估

因發生 HYCAMTIN 毒性反應而在研究期間死亡的病例：在四項肺癌試驗中接受 HYCAMTIN 膠囊治療的 682 位患者中，39 位 (6%) 在接受最後一劑藥物治療後 30 天內，因病情惡化以外的原因而死亡：13 例為血液毒性造成，5 例為非血液毒性造成（有 2 例為腹瀉造成），而 21 例為其他原因所造成。

【藥物交互作用】
Topotecan 為 P-glycoprotein(P-gp) 與乳癌抗藥蛋白 (BCRP) 之受質。這些運輸蛋白的抑制劑會升高口服 topotecan 的全身暴露量。應避免將 P-gp 抑制劑（如 amiodarone、azithromycin、captopril、carvedilol、clarithromycin、conivaptan、cyclosporine、diltiazem、dronedarone、erythromycin、felodipine、itraconazole、ketoconazole、lopinavir、ritonavir、quercetin、quinidine、ranolazine、ticagrelor、verapamil）及 BCRP 抑制劑（如 cyclosporine、eltrombopag）與 HYCAMTIN 膠囊併用（詳參臨床藥理學）。

【特殊使用族群】
【懷孕】
懷孕分級：D。
風險摘要：
對孕婦投予 HYCAMTIN 可能會導致胎兒受到傷害。對大鼠和兔子在器官形成期間投予 topotecan 會造成胚胎死亡、胎兒毒性和畸胎。如果在懷孕期間使用本藥物，或患者於使用本藥期間懷孕，應告知患者有關胎兒可能發生潛在的危險。
動物試驗的資料：
在兔子的試驗中，於懷孕第 6 天至第 20 天投予 0.10 mg/kg/day（約相當於以 mg/m² 來計算之臨床 IV 劑量）的靜脈注射 (IV) 劑量，結果會造成母體毒性、胚胎死亡及胎兒體重減輕。在大鼠的試驗中，於交配前 14 天至懷孕第 6 天投予 0.23 mg/kg/day 的 IV 劑量（約相當於以 mg/m² 來計算之臨床 IV 劑量），結果會造成胚胎再吸收、小眼症、著床前流產以及輕微的母體毒性。對大鼠於懷孕第 6 天至第 17 天投予 0.10 mg/kg/day 的 IV 劑量（約相當於以 mg/m² 來計算之臨床 IV 劑量的一半），結果會造成著床後死亡率升高。此劑量也會造成胎兒畸形總數增加。最常見的畸形係發生於眼部（小眼症、無眼症、視網膜形成玫瑰花紋、視網膜缺損、眼眶異位）、腦部（側腦室及第三腦室擴張）、頭骨與脊椎。

【授乳母親】
目前並不確知 topotecan 是否會出現於人類的乳汁。授乳大鼠會經由乳汁排出高濃度 topotecan。靜脈注射 4.72 mg/m² 劑量之雌鼠（約相當於以 mg/m² 計算之臨床靜脈注射劑量的兩倍），由乳汁排出之濃度高達血中濃度的 48 倍。由於許多藥物都會出現於人類的乳汁，且餵食母乳的嬰兒可能會因接觸 HYCAMTIN 而發生嚴重的不良反應，因此應權衡藥物對母親的重要性，然後決定是要停止餵哺母乳或是停止用藥。

【孩童】
用於孩童病患之安全及療效尚未確立。

【老年人】
在四項臨床試驗中接受 HYCAMTIN 膠囊治療的 682 位胸腔癌患者中，有 33% (n=225) 為 65 歲（含）以上，有 4.8% (n=33) 為 75 歲（含）以上。相較於 65 歲以下患者 (19%)，藥物相關腹瀉在 ≥65 歲以上患者有較高的發生率 (28%)（詳參警語及注意事項、不良反應）。
在 65 歲（含）以上的患者與較年輕的患者之間，其有效性方面並未發現任何總體性的差異。

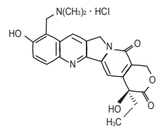
【腎功能不全】
與腎功能正常的患者相比較，在腎功能不全的患者中，topotecan lactone 與全部 topotecan 的全身暴露量都有升高現象。對輕度肾臟功能不全 (CLcr = 50-79 mL/min) 的患者，不建議調整劑量。對中度 (CLcr = 30-49 mL/min) 及重度 (CLcr< 30 mL/min) 腎功能不全的患者，應調整 HYCAMTIN 膠囊的劑量（參見劑量與用法、臨床藥理學）。

【具生育能力的女性與男性】
避孕：
女性：應和患者進行計劃懷孕與避孕方面的諮商。應囑咐具生育能力的女性患者，在使用 HYCAMTIN 治療期間應採取有效的避孕措施，在治療結束後亦應繼續避孕 1 個月。應囑咐患者，如果她們在使用 HYCAMTIN 期間懷孕或疑似懷孕，一定要和她們的健康照護人員聯繫（參見特殊使用族群）。
男性：HYCAMTIN 可能會使精子受到損傷，從而造成遺傳性畸形及胎兒畸形。應囑咐有具生育能力之女性性伴侶的男性患者，在使用 HYCAMTIN 治療期間應採取有效的避孕措施，在治療結束後亦應繼續避孕 3 個月（參見非臨床毒理）。
不孕：
女性：對具生育力的女性患者，HYCAMTIN 可能會產生急性和長期性的生育力影響（參非臨床毒理）。
男性：在投予 HYCAMTIN 的動物中曾觀察到精子生成作用受到影響的現象。應告知男性患者生育力受損的潛在風險，且在開始治療前應進行生育及家庭計畫選擇方面的諮商。

【過量】
在使用 HYCAMTIN 膠囊治療的患者中曾有用藥過量（高達處方劑量的 5 倍）的案例。用藥過量之主要併發症為骨髓抑制。用藥過量時所觀察到的徵兆與症狀和口服用之 HYCAMTIN 的已知不良反應大致相同（參見不良反應）。用藥過量時也曾有發生黏膜炎的報告。目前尚無 HYCAMTIN 用藥過量時之解毒劑。如果疑似用藥過量，應密切監視患者是否發生骨髓抑制，並視需要採取支持性的照護措施（如預防性使用 G-CSF 及 / 或抗生素治療）。

癌康定
膠囊 0.25 毫克 / 1 毫克
HYCAMTIN®
Capsules
0.25 mg, 1 mg

【性質】
Topotecan hydrochloride 為 camptothecin 之半合成衍生物，為具有 topoisomerase I 抑制活性之抗癌藥物。
Topotecan hydrochloride 之化學全名為 (*S*)-10-[(dimethylamino) methyl]-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7] indolizino [1,2-*b*]quinoline-3,14-(4*H*,12*H*)-dione monohydrochloride。其分子式為 $C_{23}H_{23}N_3O_5 \cdot HCl$，分子量為 457.9。可溶於水，分解熔點為 213°至 218°C。
Topotecan hydrochloride 之結構式如下：



口服用的 HYCAMTIN 膠囊內含 topotecan hydrochloride，其含量是以 topotecan 游離鹼基標示。賦形劑為 hydrogenated vegetable oil、glyceryl monostearate、gelatin、Purified Water 與 Preprinted hard gelatine capsule, size 2（含 titanium dioxide、red iron oxide、gelatin、black ink）。膠囊上都有用食用黑色墨水打印的標記；而 1 mg 膠囊另含有紅色氧化鐵。

【臨床藥理學】
【作用機轉】
Topoisomerase I 透過引發可逆轉之單股斷裂，減少 DNA 之旋轉壓力。Topotecan 會與 topoisomerase I-DNA 複合體結合，防止這些單股斷裂部份再度接合。Topotecan 的細胞毒性認為是來自於 DNA 合成期間，由於複製酵素與 topotecan/topoisomerase I/DNA 三元體作用，產生雙股 DNA 缺損而來。哺乳類動物細胞無法有效修復這些雙股斷裂。

【藥物動力學】
對癌症患者連續 5 天，每天投予 1.2 至 3.1 mg/m² 劑量的 HYCAMTIN 膠囊之後，topotecan 呈現雙指數藥物動力學，平均終端半衰期為 3 至 6 小時。總暴露量 (AUC) 增加幅度約與劑量成正比。
吸收：
Topotecan 在口服使用後可快速吸收，約在 1 至 2 小時內可達到最高血中濃度。Topotecan 之口服生體可用率約為 40%。食用高脂肪餐點後服用，其暴露量與空腹服用類似，但 topotecan 的 T_{max} 會從 1.5 小時延後至 3 小時，全部 topotecan lactone 的 T_{max} 則會從 3 小時延後至 4 小時 HYCAMTIN 膠囊可空腹或與食物一併服用。
分佈：
Topotecan 的血漿蛋白結合率約為 35%。
代謝：
Topotecan 之內酯 (lactone) 形式會受 pH 值影響，進行可逆之水解反應；其內酯形式具有藥理活性。在 pH≤4 時，只會存在內酯形式，而生理 pH 值下，主要會形成開放環狀之羥基酸。全部的 topotecan 及 topotecan lactone 之代謝物與母藥 AUC 的比例平均 <10%。
排泄：
針對 4 名末期實體腫瘤患者進行之質量平衡試驗中，每日使用 topotecan 5 天後，整體回收之藥物相關物質為原始口服使用劑量之 57%。尿液中，20% 之口服使用劑量以全部的 topotecan 形式排出，而 2% 則以 N-desmethyl topotecan 形式排出（詳參特殊使用族群）。糞便排出之全部的 topotecan 佔 33%，而糞便排出之 N-desmethyl topotecan 佔 1.5%。整體而言，N-desmethyl 代謝物佔尿液與糞便中藥物相關物質總量之 <6%（介於 1% 至 8%）。尿液中也發現有 topotecan 及 N-desmethyl topotecan 之 O- 葡萄糖醛酸化物 (O-glucuronides)。
特殊族群：
年齡與性別：
針對來自不同試驗的 217 名末期實體腫瘤患者分析顯示，年齡與性別不會顯著影響口服 topotecan 之藥物動力學。
種族：
就腎功能正常的患者而言，亞洲人患者 (n=7) 中的 topotecan lactone 與全部 topotecan 的暴露量（劑量變化 AUC_{inf} 的幾何平均值）各要比高加索人患者 (n=11) 高出約 30%。
就輕度腎功能不全的患者而言，亞洲人患者 (n=7) 中的 topotecan lactone 暴露量要比高加索人患者 (n=12) 高出 30%，全部 topotecan 的暴露量則大致相當。
就中度腎功能不全的患者而言，亞洲人患者 (n=8) 中的 topotecan lactone 與全部 topotecan 的暴露量都要比高加索人患者 (n=6) 高出 60%。
就重度腎功能不全的患者而言，亞洲人患者 (n=3) 中的 topotecan lactone 暴露量要比高加索人患者 (n=4) 高出 112%，全部 topotecan 暴露量則高出 70%。
腎功能不全：
曾針對 59 位晚期癌症患者進行試驗，如下表所示，接受 HYCAMTIN 膠囊治療的患者皆依據腎功能程度分群。

表 3　腎功能分群及所接受的 HYCAMTIN 初始劑量

腎功能分群	肌酸酐廓清率 (CLcr) (mL/min)	N	連續 5 天，每天一次的劑量 (mg/m²)
正常（先前未接受 P-B CT 治療）[a]	>80	6	2.3
正常（先前曾接受 P-B CT 治療）	>80	12	2.3
輕度腎功能不全	50-79	19	1.9 或 2.3
中度腎功能不全	30-49	14	1.2、1.5 或 1.8
重度腎功能不全	<30	8	0.6、0.8 或 1.2

[a] P-B CT= 含鉑化學療法。

和腎功能正常的高加索人患者相比較，輕度、中度及重度腎功能不全之高加索人患者中的 topotecan lactone 暴露量（劑量變化 AUC_{inf} 的幾何平均值）分別會升高 34%、80% 及 114%；而全部 topotecan 的對應數值分別為 70%、108% 及 227%。在輕度、中度及重度腎功能損傷的亞洲人患者中，topotecan lactone 的暴露量分別要比腎功能正常的亞洲人患者高出 34%、121% 及 247%；而全部 topotecan 的對應數值分別為 26%、153% 及 331%。在腎功能正常的患者中，先前的含鉑化學療法（P-B CT）對全部 topotecan 及 topotecan lactone 的全身暴露量皆無任何影響。
對輕度腎功能不全的患者，不建議調整劑量。對中度及重度腎功能不全的患者，應調整 HYCAMTIN 膠囊的劑量（參見劑量與用法、特殊使用族群）。
肝功能不全：
在一項針對 118 位癌症患者口服投予劑量為 0.15 至 2.7 mg/m2/day 之 topotecan 的族群藥物動力學分析中，全部 topotecan 的藥物動力學並不會因患者的血清膽紅素、ALT 或 AST 而出現明顯的差異。
藥物交互作用：
Topotecan 對藥物代謝酵素的影響：
使用已知會透過人類細胞色素 P450 (CYP1A2、CYP2A6、CYP2C8/9、CYP2C19、CYP2D6、CYP2E、CYP3A 或 CYP4A) 或二氫嘧啶脫氫酶代謝之代表受質所進行的體外抑制試驗顯示，topotecan 並不會影響這些酵素的活性。目前尚未評估過 topotecan 在活體中的酵素抑制作用。
會抑制藥物排出運輸蛋白的藥物：
將逐步提高劑量的 BCRP 與 P-gp 雙重抑制劑和口服用的 topotecan 合併投予之後，和對照組相比較，topotecan lactone 與全部 topotecan 的 AUC_{inf} 會升高約 2.5 倍（參見藥物交互作用）。於口服 topotecan 後 4 小時內口服投予 cyclosporine A（15 mg/kg）（一種 P-gp、多重抗藥蛋白 (MRP-1) 及細胞色素 P450 3A4 (CYP3A4) 的抑制劑），和對照組相比較，topotecan lactone 及全部 topotecan 的劑量標準化 $AUC_{0\text{-}24}$ 會升高 2.0 至 3.0 倍（參見藥物交互作用）。
會升高 pH 值之藥物的影響：
與 ranitidine 併用時，口服 topotecan 的藥物動力學並不會發生變化。

【非臨床毒理】
【致癌性、致突變性、生殖力損傷】
目前未進行 topotecan 之致癌症檢驗。然而，已知 topotecan 會對哺乳類動物細胞產生遺傳毒性，因此可能為致癌物。不論是否經過代謝活化，Topotecan 都會導致 L5178Y 小鼠淋巴瘤細胞突變，及導致培養之人類淋巴細胞產生畸變，也會導致小鼠骨髓產生畸變。Topotecan 不會造成細菌細胞突變。
交配前靜脈注射 1.4 mg/m² 劑量 topotecan（約相當於以 mg/m² 計算之臨床口服劑量的 0.6 倍）之雌鼠，會產生可能與透泡閉鎖抑制相關之過度排卵。若給予很少雌鼠相同劑量，也會造成胚胎植入前死亡。在大約進行試驗一個月，每日靜脈注射 0.4 mg/m² 劑量之 topotecan（約相當於以 mg/m² 計算之臨床口服劑量的 0.2 倍），認為本治療可能會造成睪丸精原巨細胞出現多核之發生率增加。Topotecan 可能會導致女性與男性生育能力受損。

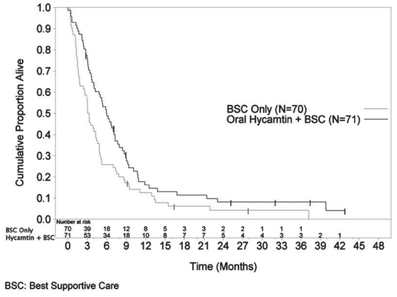
【臨床研究】
【小細胞肺癌】
曾在一項隨機分配、對照、開放試驗中，研究使用 HYCAMTIN 膠囊治療 141 位復發 SCLC 患者的療效。患者對之前的第一線化療有治療反應（完整或部份反應），經評估不適合進行標準靜脈注射化療，且在第一線化療結束至少 45 天後復發。經隨機分配，有 71 位患者接受 HYCAMTIN 膠囊（每天使用 2.3 mg/m² 之劑量，連續 5 天，每 21 天重複）及最佳支持照護 (BSC)，另有 70 位患者僅接受 BSC。主要目標為比較治療組之間的整體存活期。HYCAMTIN 膠囊加上 BSC 治療組的患者，接受療程次數之中位數為 4 個療程（介於 1 至 10 個療程），並維持 HYCAMTIN 膠囊每週 3.77mg/m² 之中位劑量強度。
HYCAMTIN 膠囊加上 BSC 組及僅使用 BSC 組之患者年齡中位數，分別為 60 歲與 58 歲，而 ≥ 65 歲患者之比例分別為 34% 與 29%。大部分的患者為高加索人 (99.3%) 及男性 (73%)。接受 HYCAMTIN 膠囊加 BSC 治療的患者有 80% 先前曾接受 carboplatin 或 cisplatin 治療，在僅使用 BSC 組中則有 77% 的患者先前曾接受 carboplatin 或 cisplatin 治療。HYCAMTIN 膠囊加上 BSC 組，包含 68% 腫瘤擴散患者，且 28% 轉移至肝臟。在僅使用 BSC 組中，61% 患者的腫瘤擴散，20% 轉移至肝臟。兩組均收錄 73% 男性。HYCAMTIN 膠囊加上 BSC 組中，18% 的患者之前使用 carboplatin，62% 之前使用 cisplatin。在僅使用 BSC 組中，26% 的患者之前使用 carboplatin，51% 之前使用 cisplatin。
HYCAMTIN 膠囊加上 BSC 組之整體存活期，在統計上顯著優於僅使用 BSC 組 (Log-rank p =0.0104)。存活期結果如表 4 及圖 1 所示。

表 4　使用 HYCAMTIN 膠囊加上 BSC 治療之小細胞肺癌患者，相較於僅使用 BSC 之整體存活期

	治療分組	
	HYCAMTIN 膠囊 + BSC (N = 71)	BSC (N = 70)
中位數（月）(95% CI)	6.0 (4.2, 7.3)	3.2 (2.6, 4.3)
危險比 (95% CI)	0.64 (0.45, 0.90)	
Log-rank p-value	0.0104	

BSC = 最佳支持照護
N = 隨機分配之患者總人數。
CI = 信賴區間。

圖 1　Kaplan-Meier 存活期估計值



BSC: Best Supportive Care

【參考文獻】
1. "OSHA HAZZRDOUS DRUGS." *OSHA*. *http://www.osha.gov/sltc/hazardousdrugs/index.html*.

【包裝規格 / 貯存及操作說明】
HYCAMTIN 0.25 毫克膠囊為不透明白色到黃白色，印有 HYCAMTIN 及 0.25 mg。
HYCAMTIN 1 毫克膠囊為不透明粉紅色，印有 HYCAMTIN 及 1 mg。
儲存於 2-8°C。請避光儲存，請將鋁箔泡囊片儲存於原裝外盒中。
HYCAMTIN 是一種細胞毒性藥物。請遵循適當的特殊操作與處理程序。[1]

【有效期限】
有效期限標示於包裝上。

【患者諮詢資訊】
- **骨髓抑制**
  應告知患者 HYCAMTIN 會降低血球計數，例如白血球、血小板與紅血球。應指示患者，若出現發燒或其他感染徵兆（如發冷、咳嗽或排尿時燒灼疼痛），應立即通知他們的醫療照護人員。應告知患者服用 HYCAMTIN 期間將頻繁進行血液檢驗，以監測是否出現骨髓抑制（參見警語及注意事項）。
- **胚胎胎兒毒性**
  應向患者提供計畫懷孕與避孕方面的建議。應囑咐具生育能力的女性患者，再使用 HYCAMTIN 治療期間應採取有效的避孕措施，在治療結束後亦應繼續避孕 1 個月（參見警語及注意事項、特殊使用族群）。
- **受乳母親**
  應囑咐患者在使用 HYCAMTIN 治療期間應停止餵哺母乳（參見特殊使用族群）。
- **不孕**
  應告知男性及女性患者潛在的生育力受損風險，以及可能的家庭計畫選擇。
- **腹瀉**
  應告知患者 HYCAMTIN 膠囊可能造成嚴重且危及生命的腹瀉。應指示患者在使用 HYCAMTIN 膠囊治療期間應如何管理及 / 或預防腹瀉，並在嚴重腹瀉發生時通知醫師（參見警語及注意事項）。

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NOVARTIS

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HYCAMTIN™ Capsules

WARNING: BONE MARROW SUPPRESSION

HYCAMTIN® can cause severe myelosuppression. Administer only to patients with neutrophil counts of ≥1,500 cells/mm^3 and platelet counts ≥100,000 cells/mm^3. Monitor blood cell counts.

1 INDICATIONS AND USAGE

HYCAMTIN capsules are indicated for the treatment of relapsed small cell lung cancer.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of HYCAMTIN capsules is 2.3 mg/m^2/day orally once daily for 5 consecutive days repeated every 21 days. Round the dose to the nearest 0.25 mg, and prescribe the minimum number of 1-mg and 0.25-mg capsules. Prescribe the same number of capsules for each of the 5 dosing days.

Take HYCAMTIN capsules with or without food. Swallow capsules whole. Do not chew, crush, or divide the capsules. Do not prescribe a replacement dose for emesis.

Diarrhea:

Do not administer HYCAMTIN capsules to patients with Grade 3 or 4 diarrhea. After recovery to Grade 1 or less, reduce the dose of HYCAMTIN by 0.4mg/m^2/day for subsequent courses *[see Warnings and Precautions (5.2)]*.

2.2 Dose Modification Guidelines

Hematologic Toxicities:

Do not administer subsequent courses of HYCAMTIN capsules until neutrophils recover to greater than 1,000 cells/mm^3, platelets recover to greater than 100,000 cells/mm^2, hemoglobin levels recover to greater than or equal to 9.0 g/dL (with transfusion if necessary).

- Dose reduce HYCAMTIN capsules by 0.4 mg/m^2/day for:
  - o neutrophil counts of less than 500 cells/mm^3 associated with fever or infection or lasting for 7 days or more;
  - o neutrophil counts of 500 to 1,000 cells/mm^3 lasting beyond day 21 of the treatment course;
  - o platelet counts less than 25,000 cells/mm^3.

Renal Impairment:

The recommended starting doses of HYCAMTIN capsules in patients with moderate and severe renal impairment are as follows:

Table 1. Dose Reduction Guidelines for Renal Impairment

Degree of Renal Impairment	Creatinine Clearance[a] (mL/min)	Dose (mg/m^2/day)
Moderate	30-49	1.5[b]
Severe	<30	0.6[b]

[a] Calculated with the Cockroft-Gault method using ideal body weight.
[b] Dose can be increased after the first course by 0.4 mg/m^2/day if no severe hematologic or gastrointestinal toxicities occur.

3 DOSAGE FORMS AND STRENGTHS

HYCAMTIN capsules contain topotecan hydrochloride expressed as topotecan free base. The 0.25-mg capsules are opaque white to yellowish-white and imprinted with HYCAMTIN and 0.25 mg. The 1-mg capsules are opaque pink and imprinted with HYCAMTIN and 1 mg.

4 CONTRAINDICATIONS

HYCAMTIN is contraindicated in patients who have a history of severe hypersensitivity reactions to topotecan.

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

Bone marrow suppression (primarily neutropenia) is a dose-limiting toxicity of HYCAMTIN. Neutropenia is not cumulative over time. The following data on myelosuppression are based on an integrated safety database from 4 thoracic malignancy trials (N = 682) using HYCAMTIN capsules at 2.3 mg/m^2/day for 5 consecutive days. The median day for neutrophil and platelet nadirs occurred on Day 15.

Neutropenia: Grade 4 neutropenia (<500 cells/mm^3) occurred in 32% of patients with a median duration of 7 days and was most common during Course 1 of treatment (20% of patients). Clinical sequelae of neutropenia included infection (17%), febrile neutropenia (4%), sepsis (2%), and septic death (1%). Pancytopenia has been reported.

Topotecan can cause fatal typhlitis (neutropenic enterocolitis). Consider the possibility of typhlitis in patients presenting with fever, neutropenia, and a abdominal pain *[see Dosage and Administration (2.2)]*.

Thrombocytopenia: Grade 4 thrombocytopenia (<10,000 cells/mm^3) occurred in 6% of patients, with a median duration of 3 days.

Anemia: Grade 3 or 4 anemia (<8 g/dL) occurred in 25% of patients.

Administer the first course of HYCAMTIN only to patients with a neutrophil count of ≥1,500 cells/mm^3 and a platelet count ≥100,000 cells/mm^3. Monitor peripheral blood cell counts frequently during treatment with HYCAMTIN. Refer to Section 2.2 for dose modification guidelines for hematological toxicities in subsequent courses.

5.2 Diarrhea

Diarrhea, including severe and life-threatening diarrhea requiring hospitalization, can occur during treatment with HYCAMTIN capsules. Diarrhea caused by HYCAMTIN capsules can occur at the same time as during-induced neutropenia and its sequelae. In the 682 patients who received HYCAMTIN capsules in the 4 lung cancer trials, the incidence of diarrhea caused by HYCAMTIN capsules was 22%, with 4% Grade 3 and 0.4% Grade 4. The incidence of Grade 3 or 4 diarrhea proximate (within 5 days) to Grade 3 or 4 neutropenia events in the group receiving HYCAMTIN capsules was 5%. The median time to onset of Grade 2 or worse diarrhea was 9 days in the group receiving HYCAMTIN capsules. Manage diarrhea caused by HYAMTIN capsules aggressively. Do not administer HYCAMTIN capsules to patients with Grade 3 or 4 diarrhea. Reduce the dose of HYCAMTIN after recovery to Grade 1 or less *[see Dosage and Administration (2.2)]*.

5.3 Interstitial Lung Disease

Interstitial lung disease (ILD), including fatalities, has occurred with HYCAMTIN. Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic radiation, and use of pneumotoxic drugs and/or colony stimulating factors. Monitor patients for pulmonary symptoms indicative of interstitial lung disease (e.g., cough, fever, dyspnea, and/or hypoxia), and discontinue HYCAMTIN if a new diagnosis of ILD is confirmed.

5.4 Embryofetal Toxicity

Pregnancy Category D

HYCAMTIN can cause fetal harm when administered to a pregnant woman. Topotecan caused embryolethality, fetotoxicity, and teratogenicity in rats and rabbits when administered during organogenesis. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use highly effective contraception during treatment and for at least 1 month after the last dose of HYCAMTIN. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking HYCAMTIN *[see Use in Specific Population (8.1, 8.7)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- **Bone Marrow Suppression *[see Warnings and Precautions (5.1)]*.**
- **Diarrhea *[see Warnings and Precautions (5.2)]*.**
- **Interstitial Lung Disease *[see Warnings and Precautions (5.3)]*.**

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of HYCAMTIN capsules was evaluated in 682 patients with lung cancer (3 recurrent small cell lung cancer [SCLS] trials and 1 recurrent non-small cell lung cancer [NSCLC] trial) who received at least one dose of HYCAMTIN capsules. Patients in all four trials had advanced lung malignancies and received prior chemotherapy in the first-line setting. The dose regimen for HYCAMTIN capsules was 2.3 mg/m^2/day for five consecutive days every 21 days. The median number of courses was 3 (range: 1 to 20) in these four trials. Table 2 describes the hematologic and non-hematologic adverse reactions in recurrent SCLC patients treated with HYCAMTIN capsules and in the overall lung cancer patient population.

Table 2. Incidence (≥5%) of Adverse Reactions in Small Cell Lung Cancer Patients Treated With HYCAMTIN Capsules Plus BSC and in Four Lung Cancer Trials

Adverse Reaction	HYCAMTIN Capsules + BSC (N = 70)			HYCAMTIN Capsules Lung Cancer Population (N = 682)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic						
Anemia	94	15	10	98	18	7
Neutropenia	91	28	33	83	24	32
Thrombocytopenia	81	30	7	81	29	6
Non-hematologic						
Nausea	27	1	0	33	3	0
Diarrhea	14	4	1	22	4	0.4
Vomiting	19	1	0	21	3	0.4
Alopecia	10	0	0	20	0.1	0
Fatigue	11	0	0	19	4	0.1
Anorexia	7	0	0	14	2	0
Asthenia	3	0	0	7	2	0
Pyrexia	7	1	0	5	1	1

BSC = Best Supportive Care.
N = total number of patients treated.
Adverse reactions were graded using NCI Common Toxicity Criteria Version 2.0.

On-Study Death Due to Toxicity of HYCAMTIN: In the 682 patients who received HYCAMTIN capsules in the four lung cancer trials, 39 deaths (6%) occurred within 30 days after the last dose for a reason other than progressive disease: 13 due to hematologic toxicity, 5 due to non-hematologic toxicity (2 from diarrhea), and 21 due to other causes.

7 DRUG INTERACTIONS

Topotecan is a substrate for both P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Inhibitors of these transporters increase the systemic exposure oral topotecan. Avoid concomitant use of P-gp inhibitors (e.g., amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltizaem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil) and BCRP inhibitors (e.g., cyclosporine, eltrombopag) with HYCAMTIN capsules *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D.

Risk Summary:

HYCAMTIN can cause fetal harm when administered to a pregnant woman. Topotecan caused embryolethality, fetotoxicity and teratogenicity in rats and rabbits when administered during organogenesis. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, inform the patient of the potential hazard to a fetus.

Animal Data:

In rabbits, an IV dose of 0.10 mg/kg/day (about equal to the clinical IV dose on a mg/m^2 basis) given on days 6 through 20 of gestation caused maternal toxicity, embryolethality, and reduced fetal body weight. In the rat, and IV dose of 0.23 mg/kg/day (about equal to the clinical IV dose on a mg/m^2 basis) given for 14 days before mating through gestation day 6 caused fetal resorption, microphthalmia, pre-implant loss, and mild maternal toxicity. Administration of an IV dose of 0.10 mg/kg/day (about half the clinical IV dose on a mg/m^2 basis) to rats on days 6 through 17 of gestation caused an increase in post-implantation mortality. This dose also caused an increase in total fetal malformations. The most frequent malformations were of the eye (microphthalmia, anophthalmia, rosette formation of the retina, coloboma of the retina, ectopic orbit), brain (dilated lateral and third ventricles), skull, and vertebrae.

8.3 Nursing Mothers

It is not known whether topotecan is present in human milk. Lactating rats excrete high concentrations of topotecan into milk. Female rats given 4.72 mg/m^2 IV (about twice the clinical dose on a mg/m^2 basis) excreted topotecan into milk at concentrations up to 48-fold higher than those in plasma. Because many drugs are present in human milk, and because of the potential for serious adverse reactions in nursing infants from HYCAMTIN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 682 patients with thoracic cancer in 4 clinical trials who received HYCAMTIN capsules, 33% (n = 225) were aged 65 years and older, while 4.8% (n = 33) were aged 75 years and older. Treatment-related diarrhea was more frequent in patients aged ≥65 years (28%) compared with those younger than 65 years (19%). *[See Warnings and Precautions (5.2), Adverse Reactions (6.1).]* Not overall differences in effectiveness were observed between patients 65 years and older and younger patients.

8.6 Renal Impairment

The systemic exposure to both topotecan lactone and total topotecan increased in patients with renal impairment compared with that in patients with normal renal function. No dosage adjustment is recommended for patients with mild renal impairment (CLcr = 50-79 mL/min). Adjust the dose of HYCAMTIN capsules in patients with moderate (CLcr = 30-49 mL/min) and severe (CLcr < 30 mL/min) renal impairment *[see Dosage and Administrating (2.2), Clinical Pharmacology (12.3)]*.

8.7 Females and Males of Reproductive Potential

Contraception:

***Female*: Counsel patients on pregnancy planning and prevention. Advise female patients of reproductive potential to use highly effective contraception during and for 1 month following treatment with HYCAMTIN. Advise patients to contact their healthcare provide if they become pregnant, or if pregnancy is suspected, while taking HYCAMTIN *[see Use in Specific Populations (8.1)]*.**

***Male*: HYCAMTIN may damage spermatozoa, resulting in possible genetic and fetal abnormalities. Advise males with a female sexual partner of reproductive potential to use effective contraception during and for 3 months after treatment with HYCAMTIN *[see Nonclinical Toxicology (13.1)]*.**

Infertility:

***Female*: In females of reproductive potential, HYCAMTIN may have both acute and long-term effects on fertility *[see Nonclinical Toxicology (13.1)]*.**

***Male*: Effects on spermatogenesis have been observed in animals administered HYCAMTIN. Advise males of the potential risk for impaired fertility and to seek counseling on fertility and family planning options prior to starting treatment.**

10 OVERDOSAGE

Overdose (up to 5-fold of the prescribed dose) occurred in patients treated with HYCAMTIN capsules. The primary complication of overdosage is bone marrow suppression. The observed signs and symptoms of overdose are consistent with the known adverse reactions associated with HYCAMTIN for oral use *[see Adverse Reactions (6.1)]*. Mucositis has also been reported in association with overdose.

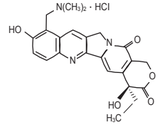
There is no known antidote for overdosage with HYCAMTIN. If an overdose is suspected, monitor the patient closely for bone marrow suppression, and institute supportive-care measures (such as the prophylactic use of G-CSF and/or antibiotic therapy) as appropriate.

11 DESCRIPTION

Topotecan hydrochloride is a semi-synthetic derivative of camptothecin and is an anti tumor drug with topoisomerase I-inhibitory activity.

The chemical name for topotecan hydrochloride is (*S*)-10-[(dimethylamino) methyl]-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7] indolizino [1,2-*b*]quinoline-3,14-(4*H*,12*H*)-dione monohydrochloride. It has the molecular formula $C_{23}H_{23}N_3O_5$•HCl and a molecular weight of 457.9. It is soluble in water and melts with decomposition at 213° to 218°C.

Topotecan hydrochloride has the following structural formula:



HYCAMTIN capsules for oral use contain topotecan hydrochloride, the content of which is expressed as topotecan free base. The excipients are gelatin, glyceryl monostearate, hydrogenated vegetable oil, Purified Water and Preprinted hard gelatin capsule, size 2 (including titanium dioxide, red iron oxide, gelatin, black ink). The capsules are imprinted with edible black ink. The 1-mg capsules also contained red iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Topoisomerase I relieves torsional strain in DNA by inducing reversible single-strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents re-ligation of these single-strand breaks. The cytotoxicity of topotecan is thought to be due to double-strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these double-strand breaks.

12.3 Pharmacokinetics

Following administration of HYCAMTIN capsules at doses of 1.2 to 3.1 mg/m^2 administered daily for 5 days. In cancer patients, topotecan exhibited biexponential pharmacokinetics with a mean terminal half-life of 3 to 6 hours. Total exposure (AUC) increased approximately proportionally to dose.

Absorption:

Topotecan is rapidly absorbed with peak plasma concentrations occurring between 1 to 2 hours following oral administration. The oral bioavailability of topotecan is approximately 40%. Following a high-fat meal, the extent of exposure was similar in the fed and fasted states, while Tmax was delayed from 1.5 to 3 hours for topotecan lactone and from 3 to 4 hours for total topotecan. HYCAMTIN capsules can be given without regard to food.

Distribution:

Binding of topotecan to plasma proteins is approximately 35%.

Metabolism:

Topotecan undergoes a reversible pH-dependent hydrolysis of its lactone moiety; it is the lactone form that is pharmacologically active. At pH ≤ 4, the lactone is exclusively present, whereas the ring-opened hydroxy-acid form predominates at physiologic pH. The mean metabolite: parent AUC ratio was <10% for total topotecan and topotecan lactone.

Excretion:

In a mass balance study in 4 patients with advanced solid tumors, the overall recovery of drug-related material following 5 daily doses of topotecan was 57% of the administered oral dose. In the urine, 20% of the orally administered dose was excreted as total topotecan and 2% was excreted as N-desmethyl topotecan *[see Use in Specific Populations (8.6)]*. Fecal elimination of total topotecan accounted for 33% while fecal elimination of N-desmethyl topotecan was 1.5%. Overall, the N-desmethyl metabolite contributed a mean of <6% (range 4 to 8%) of the total drug-related material accounted for in the urine and feces. O-glucuronides of both topotecan and N-desmethyl topotecan have been identified in the urine.

Specific Populations:

Age and Gender:

A cross-study analysis in 217 patients with advanced solid tumors indicated that age and gender did not significantly affect the pharmacokinetics of oral topotecan.

Race:

In patients with normal renal function, the exposures (geometric mean dose-normalized AUCinf) to topotecan lactone and total topotecan each were approximately 30% higher in Asian patients (n=7) compared with Caucasian patients (n=11).

In patients with mild renal impairment, the exposure was 30% higher for topotecan lactone in Asian (n=7) compared with Caucasian (n=12) patients, but the exposure to total topotecan was similar.

In patients with moderate renal impairment, the exposure was 60% higher for both topotecan lactone and total topotecan in Asian (n=8) compared with Caucasian patients (n=6).

In patients with severe renal impairment, the exposure was 112% higher for topotecan lactone and 70% higher for total topotecan in Asian (n=3) compared with Caucasian patients (n=4).

Renal Impairment:

A trial was conducted in 59 patients with advanced cancer who were grouped based on the degree of their renal function and received HYCAMTIN capsules as shown in the table below.

Table 3. Renal Function Groups With Initial Doses of HYCAMTN Received

Renal Function Group	Creatinine Clearance (CLcr) (mL/min)	N	Dose (mg/m^2) Once Daily for 5 Days
Normal (without prior P-B CT)[a]	>80	6	2.3
Normal (with prior P-B CT)	>80	12	2.3
Mild renal impairment	50-79	19	1.9 or 2.3
Moderate renal impairment	30-49	14	1.2, 1.5 or 1.8
Severe renal impairment	<30	8	0.6, 0.8 or 1.2

a P-B CT = Platinum-based chemotherapy.

The exposure (geometric mean dose-normalized AUC$_{inf}$) for topotecan lactone increased by 34%, 80%, and 114% in Caucasian patients with mild, moderate, and severe renal impairment, respectively, compared with that in Caucasian patients with normal renal function. The corresponding values for total topotecan in Caucasian patients were 70%, 108%, and 227%, respectively. Asian patients with mild, moderate, and severe renal impairment had a 34%, 121%, and 247% higher exposure to topotecan lactone, respectively, than Asian patients with normal renal function. The corresponding values for total topotecan in Asian patients are 26%, 153%, and 331%, respectively. Prior platinum-based chemotherapy (P-B CT) had no effect on the systemic exposure to both total topotecan and topotecan lactone in patients with normal renal function.

No dosage adjustment is recommended for patients with mild renal impairment. Adjust the dosage of HYCAMTIN capsules in patients with moderate and severe renal impairment *[see Dosage and Administration (2.2), Use in Specific Populations (8.6)]*.

Hepatic Impairment:

In a population pharmacokinetic analysis involving oral topotecan administered at doses of 0.15 to 2.7 mg/m^2/day to 118 cancer patients, the pharmacokinetics of total topotecan did not differ significantly based on patient serum bilirubin, ALT, or AST.

Drug Interactions:

Effects of Topotecan on Drug-Metabolizing Enzymes:

In vitro inhibition studies using marker substrates known to be metabolized by human cytochromes P450 (CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A) or dihydropyrimidine dehydrogenase indicate that the activities of these enzymes were not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated in vivo.

Drugs That Inhibit Drug Efflux Transporters:

Following coadministration of escalating doses of a dual inhibitor of BCRP and P-gp with oral topotecan, the AUC$_{inf}$ of topotecan lactone and total topotecan increased approximately 2.5-fold compared with control *[see Drug Interactions (7.1)]*.

Administration of oral cyclosporine A (15 mg/kg), an inhibitor of P-gp, multidrug-resistance-associated protein (MRP-1), and cytochrome P450 3A4 (CYP3A4) within 4 hours of oral topotecan increased the dose-normalized AUC$_{0\text{-}24h}$ of topotecan lactone and total topotecan 2.0- to 3.0-fold compared with control *[see Drug Interactions (7.1)]*.

Effect of pH-Elevating Agents:

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity testing of topotecan has not been done. Nevertheless, topotecan is known to be genotoxic to mammalian cells and is a probable carcinogen. Topotecan was mutagenic to L5178Y mouse lymphoma cells and clastogenic to cultured human lymphocytes with and without metabolic activation. It was also clastogenic to mouse bone marrow. Topotecan did not cause mutations in bacterial cells.

Topotecan given to female rats prior to mating at a dose of 1.4 mg/m^2 IV (about 0.6 times the oral clinical dose on a mg/m^2 basis) caused superovulation possibly related to inhibition of follicular atresia. This dose given to pregnant female rats also caused increased pre-implantation loss. Studies in dogs given 0.4 mg/m^2 IV (about 0.2 times the oral clinical dose on a mg/m^2 basis) of topotecan daily for a month suggest that treatment may cause an increase in the incidence of multinucleated spermatogonial giant cells in the testes. Topotecan may impair fertility in women and men.

14 CLINICAL STUDIES

14.1 Small Cell Lung Cancer

The efficacy of HYCAMTIN capsules was studied in 141 patients with relapsed SCLC in a randomized, controlled, open-label trial. The patients were prior responders (complete or partial) to first-line chemotherapy, were not considered candidates for standard intravenous chemotherapy, and had relapsed at least 45 days from the end of first-line chemotherapy. Seventy-one patients were randomized to HYCAMTIN capsules (2.3 mg/m^2/day administered for 5 consecutive days repeated every 21 days) and Best Supportive Care (BSC) and 70 patients were randomized to BSC alone. The primary objective was to compare the overall survival between the treatment arms. Patients in the arm receiving HYCAMTIN capsules plus BSC received a median of 4 courses (range: 1 to 10) and maintained a median dose intensity of, 3.77 mg/m^2/week. The median patient age in the arm receiving HYCAMTIN capsules plus BSC and the BSC-alone treatment arm was 60 years and 58 years while the percentage of patients aged ≥65 years was 34% and 29%, respectively. The majority of patients were Caucasian (99.3%) and male (73%). Eighty percent of patients receiving HYCAMTIN capsules plus BSC previously received carboplatin or cisplatin, and 77% of patients in the BSC-alone arm received prior carboplatin or cisplatin. The arm receiving HYCAMTIN capsules plus BSC included 68% of patients with extensive disease and 28% with liver metastasis. In the BSC alone arm, 61% of patients had extensive disease and 20% had liver metastases. Both treatment arms recruited 73% males. In the arm receiving HYCAMTIN capsules plus BSC, 18% of patients had prior carboplatin and 62% had prior cisplatin. In the BSC-alone arm, 26% of patients had prior carboplatin and 51% had prior cisplatin.

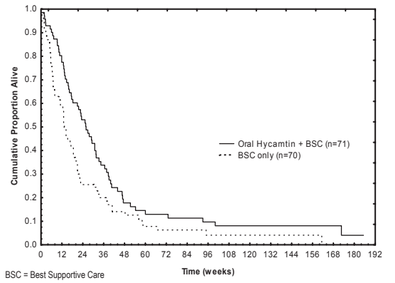
The arm receiving HYCAMTIN capsules plus BSC showed a statistically significant improvement in overall survival compared with the BSC-alone arm (Log-rank P = 0.0104). Survival results are shown in Table 3 and Figure 1.

Table 4. Overall Survival in Patients With Small Cell Lung Cancer With HYCAMTIN Capsules Plus BSC Compared With BSC Alone

	Treatment Group	
	HYCAMTIN Capsules + BSC (N = 71)	BSC (N = 70)
Median (months) (95% CI)	6.0 (4.2, 7.3)	3.2 (2.6, 4.3)
Hazard ratio (95% CI)	0.64 (0.45, 0.90)	
Log-rank P-value	0.0104	

BSC = Best Supportive Care.
N = Total number of patients randomized.
CI = Confidence interval.

Figure 1. Kaplan-Meier Estimates for Survival



BSC = Best Supportive Care

15 REFERENCE

" OSHA HAZARDOUS DRUGS " *OSHA HTTP://WWW.OSHA.GOV/SLTC/HAZARDOUSDROUGS/INDEX.HTML*

16 HOW SUPPLIED/STORAGE AND HANDLING

The 0.25-mg HYCAMTIN capsules are opaque white to yellowish-white imprinted with HYCAMTIN and 0.25 mg.

The 1 mg HYCAMTIN capsules are opaque pink imprinted with HYCAMTIN and 1 mg.

Store refrigerated 2ºC to 8ºC. Store the packages protected from light in the original outer cartons.

HYCAMTIN is a cytotoxic drug. Follow applicable special handling disposable procedures.

17 SHELF-LIFE

As registered locally.

18 PATIENT COUNSELING INFORMATION

- **Bone Marrow Suppression**

Inform patients that HYCAMTIN decreases blood cell counts such as white blood cells, platelets, and red blood cells. Instruct patients to notify their healthcare provider promptly for fever or other signs of infection such as chills, cough, or burning pain on urination. Advise patients that frequent blood tests will be performed while taking HYCAMTIN to monitor for bone marrow suppression *[see Warnings and Precautions (5.1)]*.

- **Embryofetal Toxicity**

Advise patients on pregnancy planning and prevention. Advise females of reproductive potential to use highly effective contraception during treatment and for 1 month following treatment with HYCAMTIN *[see Warnings and Precaution (5.6), Use in Specific Population (8.1, 8.7)]*.

Advise males with a female sexual partner of reproductive potential to use effective contraception during and for 3 months after treatment *[see Nonclinical Toxicology (13.1)]*.

- **Nursing Mothers**

Advise patients to discontinue nursing during treatment with HYCAMTIN *[see Use in Specific Populations (8.1, 8.7)]*.

- **Infertility**

Advise male and female patients of the potential risk for impaired fertility and possible family planning options.

- **Diarrhea**

Inform patients that HYCAMTIN capsules cause diarrhea which may be severe and life-threatening. Instruct patients how to manage and/or prevent diarrhea and to inform their physician if severe diarrhea occurs during with HYCAMTIN capsules *[see Warnings and Precautions (5.2)]*.

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