



Therapeutic Class ReviewSM

Antineoplastics – topotecan capsules (Hycamtin[®])

December 2008

New Product for Review:

topotecan capsules (Hycamtin[®]) [GSK]

Dossier Provided by Manufacturer: No

Dossier Evaluation: N/A

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

Executive Summary

Small Cell Lung Cancer (SCLC):

- Small cell lung cancer (SCLC) is the most aggressive pulmonary tumor. ^[1]
 - SCLC is more likely to be widely disseminated at the time of diagnosis than other pulmonary tumors.
 - Median survival from diagnosis is about 2 to 4 months without treatment.
- Current chemotherapy regimens can prolong median survival by 4- to 5-fold over patients who receive no therapy. ^[1]
- Primary chemotherapy for patients with SCLC generally includes a platinum-based intravenous regimen.

Topotecan (Hycamtin):

- Topotecan (Hycamtin) injection was approved in May 1996 and is covered under the medical benefit.
- The oral formulation of topotecan (Hycamtin) was approved by the FDA in October 2007 (however, not commercially available until September 2008) and is covered under the prescription benefit.
- The two formulations of topotecan (Hycamtin) differ in their dosing and FDA-approved indications:

	Topotecan oral capsules	Topotecan injection
Dose:	2.3 mg/m ² /day	0.75 to 1.5 mg/m ² /day

Administration:	Oral without regard to meals	Intravenous infusion over 30 min
FDA-approved indications:	Relapsed SCLC	Ovarian cancer (second-line) SCLC (second-line) Relapsed cervical cancer

- Caution is urged when switching from oral to intravenous topotecan due to differences in dosing between the two formulations.
- National guidelines list single-agent topotecan (Hycamtin) as one of several possible treatment options for the treatment of SCLC (there is no specific recommendation regarding route of administration).
- Potential off-label uses of oral topotecan include second-line treatment of ovarian and cervical cancers.

Evidence

- There is no reliable evidence that supports the efficacy of oral topotecan (Hycamtin) in the treatment of SCLC, NSCLC, or ovarian carcinoma.
 - None of the trials were blinded (open-label design).
 - Flaws included large numbers of non-completers, confounding chemotherapy regimens and poorly described randomization methods.
- Trials comparing oral and intravenous formulations of topotecan were not blinded and used poorly defined methods for measuring tumor response (the primary endpoint).

Decision

Oral topotecan (Hycamtin) is preferred/formulary because, although the evidence comparing this product to other treatment alternatives is uncertain, it may provide benefit to certain members, particularly those living in rural areas who must commute long distances to receive treatment.

Products

Drug Products	FDA approval ^a	Patent Expiration(s) ^b	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
topotecan injection (Hycamtin [®]) ^[3]	5/1996	10/2010	<ul style="list-style-type: none"> ▪ Metastatic ovarian cancer after failure of initial chemotherapy ▪ Small cell lung cancer after failure of first-line chemotherapy ▪ Stage IV-B, recurrent, or persistent cervical cancer not amenable to curative treatment with surgery and/or radiation 	<p><i>Ovarian and small cell lung cancer:</i> 1.5 mg/m²/day intravenously over 30 minutes once daily for 5 days, every 21 days</p> <p><i>Cervical cancer:</i> 0.75mg/m² intravenously over 30 minutes daily on days 1, 2, & 3, every 21 days</p>	Chronic myelogenous leukemia, primary CNS lymphoma, myelodysplastic syndrome, nephroblastoma, non-small cell lung cancer
topotecan oral capsules (Hycamtin [®]) ^[2]	10/2007	11/2010	<ul style="list-style-type: none"> ▪ Relapsed small cell lung cancer 	2.3 mg/m ² /day orally once daily for 5 days, every 21 days	Ovarian cancer, cervical cancer

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Based on patents listed in Orange Book as of 05/06/08.

^c As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

References

1. U.S. National Institutes of Health, National Cancer Institute [page on the internet]. Small cell lung cancer treatment (PDQ[®]). Available at: <http://www.cancer.gov/cancertopics/pdq/treatment/small-cell-lung/HealthProfessional/page2>. Accessed on 5/28/2008.
2. Hycamtin[®] oral capsules (topotecan) prescribing information. GlaxoSmithKline: Research Triangle Park, NC; October 2007.
3. Hycamtin[®] injection (topotecan) prescribing information. GlaxoSmithKline: Research Triangle Park, NC; August 2007.
4. O'Brien ME, Ciuleanu TE, Tsekov H, Shparyk Y, Cuceviá B, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol.* 2006;24(34):5441-7.
5. Eckardt JR, von Pawel J, Pujol JL, Papai Z, Quoix E, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol.* 2007;25(15):2086-92. Erratum in: *J Clin Oncol.* 2007;25(22):3387.
6. Eckardt JR, von Pawel J, Papai Z, Tomova A, Tzekova V, et al. Open-label, multicenter, randomized, phase III study comparing oral topotecan/cisplatin versus etoposide/cisplatin as treatment for chemotherapy-naïve patients with extensive-disease small-cell lung cancer. *J Clin Oncol.* 2006;24(13):2044-51.
7. von Pawel J, Gatzemeier U, Pujol JL, Moreau L, Bildat S, et al. Phase II comparator study of oral versus intravenous topotecan in patients with chemosensitive small-cell lung cancer. *J Clin Oncol.* 2001; 19(6):1743-9.
8. Ramlau R, Gervais R, Krzakowski M, von Pawel J, Kaukel E, et al. Phase III study comparing oral topotecan to intravenous docetaxel in patients with pretreated advanced non-small-cell lung cancer. *J Clin Oncol.* 2006;24(18):2800-7. Epub 2006 May 8.
9. Gore M, Oza A, Rustin G, Malfetano J, Calvert H, et al. A randomized trial of oral versus intravenous topotecan in patients with relapsed epithelial ovarian cancer. *Eur J Cancer.* 2002;38(1):57-63.
10. Peng LH, Chen XY, Wu TX. Topotecan for ovarian cancer. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD005589. DOI: 10.1002/14651858.CD005589.pub2.

11. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer v.2.2009. Available at: http://www.nccn.org/professionals/physician_gls/PDF/sclc.pdf. Accessed on 11/19/08.
12. National Cancer Institute. Quick reference: Response evaluation criteria in solid tumors (RECIST). Available at <http://ctep.cancer.gov/forms/quickrcst.doc>. Accessed on 5/15/2008.