



**Attachment I**

**Irinotecan Hydrochloride Injection, 20 mg/mL**

**Medical Rationale**

Mayne Pharma provides the following information as medical rationale for the addition of a 500 mg/25 mL presentation of Irinotecan Hydrochloride Injection.

### **INDICATIONS AND USAGE**

Camptosar<sup>®</sup> Injection is indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. Camptosar<sup>®</sup> is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

### **CLINICAL PHARMACOLOGY**

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. In vitro cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold. However, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan (see Pharmacokinetics). The precise contribution of SN-38 to the activity of Camptosar<sup>®</sup> is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types.

#### **Pharmacokinetics**

After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38

are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the recommended dosage range of 50 to 350 mg/m<sup>2</sup>, the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan. Pharmacokinetic parameters for irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and 340 mg/m<sup>2</sup> determined in two clinical studies in patients with solid tumors are summarized in Table 1 (extracted from the package insert of the reference listed drug):

<b>Table 1. Summary of Mean (± Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients with Solid Tumors</b>								
Dose (mg/m <sup>2</sup> )	Irinotecan					SN-38		
	C <sub>max</sub> (ng/mL)	AUC <sub>0-24</sub> (ng·h/mL)	t <sub>1/2</sub> (h)	V <sub>z</sub> (L/m <sup>2</sup> )	CL (L/h/m <sup>2</sup> )	C <sub>max</sub> (ng/mL)	AUC <sub>0-24</sub> (ng·h/mL)	t <sub>1/2</sub> (h)
125 (N=64)	1,660 ±797	10,200 ±3,270	5.8 <sup>a</sup> ±0.7	110 ±48.5	13.3 ±6.01	26.3 ±11.9	229 ±108	10.4 <sup>a</sup> ±3.1
340 (N=6)	3,392 ±874	20,604 ±6,027	11.7 <sup>b</sup> ±1.0	234 ±69.6	13.9 ±4.0	56.0 ±28.2	474 ±245	21.0 <sup>b</sup> ±4.3
C <sub>max</sub> - Maximum plasma concentration								
AUC <sub>0-24</sub> - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion								
t <sub>1/2</sub> - Terminal elimination half-life								
V <sub>z</sub> - Volume of distribution of terminal elimination phase								
CL - Total systemic clearance								
<sup>a</sup> Plasma specimens collected for 24 hours following the end of the 90-minute infusion.								
<sup>b</sup> Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate of the terminal elimination half-lives of irinotecan and SN-38.								

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

## **DOSAGE AND ADMINISTRATION**

### **Single-Agent Dosage Schedules**

The Package insert of the Referenced Listed Drug states that:

#### ***Dosage Regimens***

CAMPTOSAR should be administered as an intravenous infusion over 90 minutes for both the weekly and once-every-3-week dosage schedules (see Preparation of Infusion

Solution). Single-agent dosage regimens are shown in Table 12, extracted from the package insert of the reference listed drug.

Table 12. Single-Agent Regimens of CAMPTOSAR and Dose Modifications			
Weekly Regimen <sup>a</sup>	125 mg/m <sup>2</sup> IV over 90 min, d 1,8,15,22 then 2-wk rest		
Starting Dose & Modified Dose Levels <sup>c</sup> (mg/m <sup>2</sup> )			
Starting Dose	Dose Level -1	Dose Level -2	
125	100	75	
Once-Every-3-Week Regimen <sup>b</sup>	350 mg/m <sup>2</sup> IV over 90 min, once every 3 wks <sup>c</sup>		
Starting Dose & Modified Dose Levels (mg/m <sup>2</sup> )			
Starting Dose	Dose Level -1	Dose Level -2	
350	300	250	
<sup>a</sup> Subsequent doses may be adjusted as high as 150 mg/m <sup>2</sup> or to as low as 50 mg/m <sup>2</sup> in 25 to 50 mg/m <sup>2</sup> decrements depending upon individual patient tolerance.			
<sup>b</sup> Subsequent doses may be adjusted as low as 200 mg/m <sup>2</sup> in 50 mg/m <sup>2</sup> decrements depending upon individual patient tolerance.			
<sup>c</sup> Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.			

## RATIONALE AND SUMMARY

The currently marketed Reference Listed Drug (Camptosar®) is available in two presentations, 40 mg/2 mL and 100 mg/5 mL. As indicated in the dosage and administration sections of the approved package insert for Camptosar®, as a single agent, irinotecan hydrochloride injection has been shown to be effective in patients with metastatic carcinoma of the colon or rectum. Based upon the recommended starting dose of 350 mg/m<sup>2</sup> (595 mg for the average 1.7 m<sup>2</sup> body), Mayne proposes the additional presentation of 500 mg/25 mL which would provide for ease of administration through less vials, less chance for contamination and less hazardous waste, as well as a reduction in cost for the course of therapy. The average initial dose of 595 mg would require only two vials (one 500 mg/25 mL and one 100 mg/5 mL) instead of six 100 mg/5 mL vials. Similarly, the modified dose regimen of 300 mg/m<sup>2</sup> would benefit from the use of a 500 mg/25 mL vial.