CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20449/S11

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEC 15 1999 Staten

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

sNDA:	20-449/011
Submission Date:	November 29, 1999
Drug Name:	Taxotere® (Docetaxel)
Formulation:	40 mg/ml Docetaxel (Anhydrous) in Single-Dose Vials For Intravenous Injection
Sponsor:	Rhone-Poulenc Rorer Pharmaceuticals Inc. Collegeville, PA
Reviewer:	Safaa Ibrahim, Ph.D.
Submission Type:	Review of Drug Interactions data

This submission is in response to the OCPB' Comment that was faxed to the sponsor on November 3, 1999 for docetaxel. The sponsor was requested to provide information regarding the potential for drug-drug interactions between Taxotere® and other drugs commonly prescribed to 1st- and 2nd -line non-small cell lung cancer (NSCLS) patients.

Docetaxel (Taxotere®) is a semisynthetic member of the taxoid family originally synthesized

Docetaxel is mainly eliminated by hepatic metabolism and only a minor fraction of the dose is excreted as a parent drug. The main enzymes involved in docetaxel metabolism are monooxygenases. Conjugation of the parent drug and metabolites appeared to be of very minor importance. In human liver microsomes, cytochrome P-450 isoenzymes of the CYP3A subfamily were mainly responsible for docetaxel biotransformation. Docetaxel was metabolized with a Km of 1.1 μM and a Vmax of 9.2 pmol/min/mg protein. In addition docetaxel is extensively bound to plasma proteins. *In vitro* plasma protein binding is 94 % at clinical drug concentrations. The main proteins involved are albumin, α1-acid glycoprotein and lipoproteins. A binding of 97.8 % was measured *in vivo* in 3 cancer patients.

The sponsor submitted on June 23 and 30, 1999 a supplemental New Drug Application (sNDA) for the use of Taxotere® as a first- and second-line therapy in the treatment of patients with **non-small cell lung cancer**. The optimal dosing

schedule for this patient population is 60-75 mg/m^2 administered as a one-hour intravenous infusion on day one of a 21-day cycle.

Human pharmacokinetics data submitted for this sNDA were reviewed in the submissions of September 2 and October 26, 1999. These submissions did not include any information on the possible drug-drug interactions between Taxotere® and commonly prescribed drugs in NSCL patients.

The present submission contains *in vitro* metabolic inhibition studies and *in vitro* protein binding displacement studies to provide some information on the potential for drug-drug interactions between Taxotere® and commonly prescribed drugs. In addition, a summary of a literature search was also submitted.

Review of *In Vitro* Metabolic Inhibition studies:

The effect of several specific inhibitors of cytochrome P450 isoenzymes and drugs on docetaxel biotransformation in human liver microsomes was studied at a docetaxel concentration of 5 μM.

Tables 1 and 2 show the results of these *in vitro* microsomal studies.

Table 1. Effect of cytochrome P450 substrates/inhibitors on docetaxel biotransformation in human liver microsomes.

[IC50 = concentration inhibiting docetaxel biotransformation rate at 5 μM by 50%]

Compound	μM	specificity	% control	IC50 (μM)
Caffeine	400	CYP1A	77	
Acetanilide	1000	CYP1A	87	
a-naphthoflavone	1	CYP1A	101	
Aniline	50	CYP2E	82	
SKF 525A	250	several	60	
Tolbutamide	50	CYP2C	111	
Quinidine	5	CYP2D6	107	
Erythromycin	1000	CYP3A	47	
Troleandomycin	1-1000	CYP3A		10
Nifedipine	10-1000	CYP3A		130
Ketoconazole	1-10	CYP3A		~ 1

From Table 1, it is seen that ketoconazole, troleandomycin, nifedipine and erythromycin were able to inhibit docetaxel biotransformation, indicating a major role of P450 isoenzymes of the CYP3A subfamily in human metabolism. Substrates and/or inhibitors of other isoenzymes had no effect.

Table 2. Effect of other drugs on docetaxel biotransformation in human liver microsomes.

Compound	Range (μM)	IC50 (μM)
Ranitidine	1-1000	n.e.
Cimetidine	1-1000	n.e.
Omeprazole	1-100	n.e.
Imipramine	1-100	n.e.
Diazepam	1-100	n.e.
Paracetamol	1-1000	n.e.

n.e.= no effect.

The anti-H_2 drugs, cimetidine, ranitidine and omeprazole and also diazepam, imipramine and paracetamol had no effect on the metabolism of docetaxel.

Review of *In Vitro* Protein Binding Displacement studies:

The effect of erythromycine, salicylate, sufamethoxazole, diphenhydramine, propranolol, propafenone, phenytoin and sodium valproate at their therapeutic concentrations on the protein binding of docetaxel was studied using ultrafiltration technique. The effect of docetaxel on ^{3}H-digitoxin serum binding was also studied. The results of these studies are shown in Tables 3 and 4.

Table 3· Effect of drugs on mean docetaxel (5 pg/ml) serum binding (expressed in %)

Serum	Concentration	Mean	SD	N
Control	5 μg/ml	93.4	6.0	29
Erythromycine	7 μg/ml	92.7	3.3	10
Salicylate	300 μg/ml	91.4	7.0	10
Sufamethoxazole	60 μg/ml	91.6	8.4	15
Diphenhydramine	100 ng/ml	89.5	8.4	10
Propranolol	900 ng/ml	96.3	3.1	10
Propafenone	3 μg/ml	90.1	10.6	10
Phenytoin	15 μg/ml	89.7	7.3	9
Sodium valproate	100 μg/ml	91.1	13.3	10

SD: standard deviation, N: number of replicates.
ANOVA, F(8,104 D.F.)=0.83, P= 0.57, no significant differences between docetaxel serum binding percentages (versus control).

Table 4. Effect of docetaxel on mean ^{3}H-digitoxin (25 ng/ml) serum binding (expressed in %)

Serum	Concentration	Mean	SD	N
Control	25 ng/ml	98.1	2.4	5
Docetaxel	5 μg/ml	95.4	6.8	5

SD: standard deviation, N: number of replicates.
ANOVA, F(1,8 D.F.)=0.72, P= 0.42, no significant differences between ^{3}H-digitoxin serum binding percentages (versus control).

From the above tables, it is seen that at therapeutic concentrations, drugs such as erythromycine, salycilate, sufamethoxazol, propranolol, propafenone, and sodium valproate, have no effect on the protein binding of docetaxel, i.e., no displacement of docetaxel from protein binding sites occurred. Diphenhydramine and phenytoin may have an effect on docetaxel protein binding; the % protein bound of docetaxel decreased from 93.4% to 89.5% and 89.7%, respectively. The clinical significance of this displacement interaction is not known.

Docetaxel has no effect on the protein binding of digitoxin. No digitoxin displacement was observed by docetaxel.

Review of Literature Search:

A search in the clinical database was performed to identify concurrent medications actually prescribed to patients with both previously untreated or first-line (study 308) and previously treated or second (study 317 and study 320) patients with NSCLC. The search was limited to the drugs administered the day of docetaxel infusion at least once during the treatment (i.e. the drugs at risk for interaction). A literature search was performed on the clinical database to assess the potential for metabolic drug-drug interactions with docetaxel of the drugs given to > 10 % of the patients. The assessment was based on the following drug characteristics:

- Involvement of CYP3A in the metabolism of the drug co-administered with docetaxel and Km if available.

- Inhibition of CYP3A by the drug co-administered (even if not metabolized by CYP3A) and Ki if available.

- Therapeutic plasma levels of the drug co-administered.

The results of this analysis are reported in Table 5 (first line patients) and Table 6 (second line patients). Attachment 1 shows Comment's and reference's number as indicated in Tables 5 and 6.

Appendix

5

Table 4. Drugs commonly administered to patients with first line NSCLC (study 308) and their potential for metabolic interaction with docetaxel.

Drug	n (%)	CYP 3A		Plasma levels	Interaction potential (comment number)	
		Involved (Km)[ref]	Inhibit (Ki)		May inhibit Docetaxel	May be inhibited by Docetaxel
Ranitidine	32 (23.2)	not known	no[1,2]	1.5 µM[3]	unlikely (a)	unlikely (b)
Tramadol	18 (13.0)	possibly (c)	not known	1.9 µM (PDR)	not known	not known
Bromhexine	16 (11.6)	no relevant data	no relevant data	0.09 µM[4]	not known	not known Clinical consequences of any inhibition unlikely (large therapeutic margin)
Morphine	15 (10.9)	unlikely (d)	no (d and PDR)	0.035-0.25 µM (PDR)	unlikely	unlikely

PDR: Physicians' Desk Reference, 1998, edition 52.

Table A2. Drugs commonly administered to patients with second line NSCLC (study 317 and study 320) and their potential for metabolic interaction with docetaxel.

Drug	n (%)	CYP 3A		Plasma levels	Interaction potential (comment number)	
		involved (Km)[ref]	Inhibited (Ki)		May inhibit Docetaxel	May be inhibited by Docetaxel
Granisetron	68 (19.7)	yes (4 µM)[5]	unlikely (e)	0.026 µM (Clarke's)	unlikely	possibly
Ondansetron	68 (19.7)	yes[6]	yes (31 µM)[7]	0.5 µM (PDR)	unlikely	possibly, but with no PD consequences (PDR)
Prochlorperazine	53 (15.3)	not known	not known	0.25 - 3 µM[8]	may inhibit PGP-dependent efflux of docetaxel	not known
Diphenhydramine	52 (15.0)	not known	not known	0.4 - 4 µM (Clarke's)	not known	not known
Morphine	44 (12.2)	unlikely (d)	no (PDR)	0.035-0.25 µM (PDR)	unlikely	unlikely

PDR: Physicians' Desk Reference, 1998, edition 52.
Clarke's Isolation and Identification of Drugs, 1986, 2nd edition, Pharmaceutical Press, London

From Tables 5 and 6, it is seen that most drugs that were coadministered with docetaxel to NSCLC patients during Phase III clinical trials (i.e., given to 10 % or more of the patients) may unlikely to interact with docetaxel (e.g., ranitidine and morphine). In other cases (e.g., tramadol and diphenhydramine), the possibility of interaction is not known.

LABELING COMMENTS

1. The following statement should be added the "CLINICAL PHARMACOLOGY" section of the package insert for Taxotere®:

"*In vitro* drug interaction studies reveal that docetaxel is metabolized by CYP3A4. Therefore, metabolism of docetaxel can be inhibited by the CYP3A4 inhibitors such as ketoconazole, erythromycin, troleandomycin, nifedipine. No clinical studies have been performed to evaluate this finding. Based on the *in vitro* findings, 3A4 inhibitors and/or substrates may lead to substantial increase in docetaxel blood concentrations. (see PRECAUTIONS)"

RECOMMENDATION

The sponsor is recommended to incorporate the above labeling Comment in the current package insert for Taxotere®.

Please forward the above Recommendation and Comment to the sponsor.

/S/ 12/15/99
Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

/S/
Reviewer: Safaa Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

cc: sNDA 20-449
HFD-150/Division file
HFD-150/Staten, Beitz, Griebel
HFD-850/Lesko
HFD-860/Mehta, Rahman, Ibrahim
CDR (Biopharm)

Attachment 1

Comments

a - PDR 1998 stipulates, page 1127 in the Drug Interactions section, that "Although ZANTAC has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended dose of the drug do not inhibit the action of cytochrome P-450-linked oxygenase in the liver."

b - Enzymes involved in phase I metabolism of ranitidine seems not described in the literature. PDR 1998 indicates, page 1129, in the Pharmacokinetics section, that "The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected as unchanged drug in 24 hours." This hydrophilic compound (freely soluble in water - Merk Index 1996) is therefore not expected to be susceptible to be inhibited by docetaxel via CYP3A.

c - PDR 1998 notes, page 2065, in the Drug Interactions chapter, that "Concomitant administration of ULTRAM (tramadol) with carbamazepine causes a significant increase in tramadol metabolism, presumably through metabolic induction by carbamazepine." Since carbamazepine is an inducer of P450s such as CYP3A, this might be indicative of a CYP3A involvement in tramadol metabolism.

d - We did not find studies on morphine-related P450 metabolism nor on P450s inhibition by morphine. However, morphine is 60-70% metabolized by direct 3- and 6-glucuronidation, and excreted in the urine. Direct 3-sulfoconjugation also occurs. Phase I N-desmethylation, N-oxidation and O-methylation represents less than 5%. Therefore, inhibition of CYP3A is not expected to alter morphine clearance.

e - In reference 6, granisetron up to 250 μM did not inhibit the CYP3A-dependent testosterone 6β-hydmxylation in three different liver microsomes. However, the authors used 250 pM testosterone. This is about 3-fold the Km value of testosterone 6β-hydroxylase, and we think that inhibition of CYP3A by granisetron could have been underestimated in this design. The low Km value (4 pM) of granisetron metabolism by CYP3A also is in favor of a likely competitive inhibitory effect of granisetron, as a substrate, on CYP3A.

References

1. Martinez C. et al. Comparative *in vitro* and *in vivo* inhibition of cytochrome P450 CYP1A2, CYP2D6 and CYP3A by H2receptor antagonists. Clin Pharmacol Ther, 64:369-376, 1999.

2. Marre F. et al. Hepatic biotransformation of docetaxel (Taxotere®) *in vitro*: involvement of the CYP3A subfamily in humans. Cancer Research, 56:1296-1302,1996.

3. Castaneda H.G. et al. Pharmacokinetics of oral ranitidine in Mexicans. Arch Med Res, 27:349-352,1996.

4. Bechgaard E. et al. Bioavailability of bromhexine tablets and preliminary pharmacokinetics in humans. Biopharm Drug Dispo, 3:337-344,1982.

5. Bloomer J.C. and al. Characterization of the cytochrome P450 enzymes involved in the *in vitro* metabolism of grenisetron. Br J Clin Pharmacol, 38:557-566,1994.

6. Dixon C.M. et al. Multiple forms of CYP450 are involved in the metabolism of ondansetron in humans. Drug Metab Dispos, 23:1225-1230,1996.

7. Fischer V. at al. The polymorphic CYP2D6 is involved in the metabolism of both 5-hydroxytriptamine antagonists, tropisetron and ondansetron. Drug Metab Dispo, 22: 269-274,1994.

8. Sridhar K.S. at al. Prechlorperazine as a doxorubicin-effiux blocker: phase I clinical and pharmacokinetics studies. Cancer Chemother Pharmacol, 3: 423-430,1993.

NOV 2 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

sNDA:	20-449/011
Submission Dates:	September 2, 1999 October 26, 1999
Drug Name:	Taxotere® (Docetaxel)
Formulation:	40 mg/ml Docetaxel (Anhydrous) in Single-Dose Vials For Intravenous Injection
Sponsor:	Rhone-Poulenc Rorer Pharmaceuticals Inc. Collegeville, PA
Reviewer:	Safaa Ibrahim, Ph.D.
Submission Type:	Review of Pharmacokinetic data

This submission is in response to OCPB' Comments that were faxed to the sponsor on August 11, 1999 for docetaxel.

Docetaxel (Taxotere®) is a semisynthetic member of the taxoid family originally synthesized from

The sponsor submitted on June 23 and 30, 1999 a supplemental New Drug Application (sNDA) for the use of Taxotere® as a first- and second-line therapy in the treatment of patients with **non-small cell lung cancer**. The optimal dosing schedule for this patient population is 60-75 mg/m^2 administered as a one-hour intravenous infusion on day one of a 21-day cycle. No human pharmacokinetics data was submitted in this sNDA and no changes were made in the Clinical Pharmacology/Pharmacokinetics section of the current package insert for Taxotere® (see Attachment 1). Therefore, in the review of this sNDA, the sponsor was recommended to submit any pharmacokinetic information for docetaxel in patients with non-small cell lung cancer at the proposed dosing schedule of 60-75 mg/m^2. The sponsor was also recommended to provide any information on the potential for drug-drug interactions between docetaxel and other drugs that are commonly prescribed to patients with non-small cell lung cancer.

The current submission contains the population pharmacokinetic analysis report that was previously submitted in the original NDA for Taxotere® on July 27, 1994. This report describes the population (NONMEM) analysis of pharmacokinetic

data obtained in Phase I and Phase II studies from 547 patients with a variety of tumor types including breast and non-small-cell lung cancer (NSCL) at the first cycle of treatment. Phase I patients received 70-115 mg/m^2 docetaxel as 1- to 2-hour infusions and were extensively sampled (9-15 samples per patient). Phase II patients received 75 mg/m^2 (28 patients) or 100 mg/m^2 (493 patients) docetaxel as a 1-hour infusion. A sparse sampling strategy was implemented in Phase II studies (3 samples per patient). The model building and validation of PK data were reviewed and provided in the original NDA submission (dated July 27, 1994). The final PK model revealed that five covariates were important predictors of clearance (CL) of docetaxel and hence its exposure (AUC). The three main predictors were body surface area (BSA), baseline α_1-glycoprotein level (AAG), and hepatic function (HEP). Age (AGE) and albumin level (ALB) had significant but minor effect on docetaxel CL. The final model is as follows:

$$CL=BSA\ (22.1-3.55AAG-0.095AGE+0.225ALB)\ (1-0.334HEP)$$

Using the final PK model, the sponsor obtained Bayesian estimates for individual CL values (L/hr). These individual CL values were stratified by tumor type and summarized in the table below (see also Attachment 2):

Mean (SD) CL by Tumor Type

Tumor Type	N	CL (L/hr)
Breast	168	37.8 (11.8)
NSCL	189	37.04 (12.4)
Colorectal	59	36.9 (14.8)
Melanoma	29	34.8 (11.8)
SCL	26	34.05 (11.8)
Renal	21	36.4 (15.5)
Head & Neck	28	31.5 (9.2)
Gastric	31	33.2 (9.8)
Sarcoma	16	42.3 (12.5)
Ovarian	10	41.7 (15.6)

From the above table, it can be seen that CL estimates and variability are similar among tumor types. The slightly higher CL values for patients with sarcoma and ovarian cancer may be due to the smaller sample size in the PK database, N =16 and 10, respectively, compared with other tumor types (N=21-189). It is noticed that in this analysis, most NSCL cancer patients were administered a higher dose (100 mg/m^2) than the recommended dose (60-75 mg/m^2). However, this does not matter since docetaxel displays linear kinetics over the dosage range of 70-115 mg/m^2 and thus, docetaxel clearance is independent of dose.

It can be concluded that the pharmacokinetics of docetaxel are not affected by tumor type at the therapeutic dosing range.

COMMENTS

1. The sponsor should incorporate the following statement in the **current** package insert for Taxotere®, under CLINICAL PHARMACOLOGY/ HUMAN PHARMACOKINETICS (Page 4, third paragraph):

"In addition, population pharmacokinetic analysis revealed that patients with different tumor types had similar clearance values, indicating that the elimination of docetaxel is not affected by tumor type".

2. The sponsor has not yet addressed the potential for drug-drug interactions between docetaxel and other drugs that are commonly prescribed to patients with non-small cell lung cancer.

RECOMMENDATION

Please forward the above Comments to the sponsor.

/S/ 11/2/99

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

/S/

Reviewer: Safaa Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

Redacted 30

pages of trade

secret and/or

confidential

commercial

information

Attachment 1 - Draft Labeling

Attachment 1

Table 2 : RP 56976 (docetaxel) population PK analysis (Phase II studies) :
Summary of Phase II patients available for the different steps of the population PK/PD analysis

Study	Section	Evaluable for PK/PD	Population PK		Additional Patients For PK/PD
			Model Building	Validation	
	Breast				
221	pivotal (Eur.)	26	23	3	0
233	(USA)	31	15	13	3
267	(USA)	27	14	11	2
237	suppor. (Eur.)	27	25	2	0
266	(USA)	35	8	17	10
280	(Eur.)	22	17	3	2
		168	102	49	17
	NSCL				
270	pivotal (USA)	22	4	13	5
271	(USA)	30	14	14	2
223	(Eur.)	37	34	3	0
231	(USA)	38	14	17	7
232	(USA)	31	6	24	1
269	(USA)	31	3	21	7
		189	75	92	22
	Safety				
220	Colorectal (Eur.)	32	26	5	1
222	Melanoma (Eur.)	29	0	28	1
224	SCL (Eur.)	26	24	2	0
225	Renal (Eur.)	21	0	18	3
227	Head&Neck (Eur.)	28	5	19	4
230	Colorectal (USA)	18	5	12	1
236	Gastric (Eur.)	31	0	30	1
245	Sarcoma (Eur.)	16	0	11	5
252	Ovarian (USA)	10	9	0	1
257	Colorectal (USA)	9	8	1	0
		220	77	126	17
Total	Europe	295	154	124	17
	USA	282	100	143	39
	Overall	577	254	267	56

6-29-55

Pharmacokinetic parameter estimates for 11 PK analysis (n=477 patients)

Study=233

OBS	Study	ID	CL1 (l/h)	CL2 (l/h)	CL3 (l/h)	CL1* (l/h)	f1	f2	f3	f4	fu	AUC (ug/ml*h)
287	233	601										
288	233	602										
289	233	603										
290	233	604										
291	233	605										
292	233	606										
293	233	607										
294	233	608										
295	233	609										
296	233	610										
297	233	611										
298	233	612										
299	233	613										
300	233	614										
301	233	616										
302	233	617										
303	233	620										
304	233	621										
305	233	622										
306	233	623										
307	233	624										
308	233	625										
309	233	626										
310	233	627										
311	233	628										
312	233	630										
313	233	631										
314	233	632										
315	233	633										
316	233	634										
317	233	635										

N=31

Breast

Pharmacokinetic parameter estimates for [illegible] analysis (n=577 patients)

Study 266

OBS	Study	ID	CL/F (l/h)	CLcr (l/h)	$\widehat{CL/F}$ (l/h)	$\widehat{CL/F}^*$ (l/h)	f1	f2	f3	f4	fu	AUC (ug/ml*h)
411	266	201										
412	266	202										
413	266	203										
414	266	204										
415	266	205										
416	266	206										
417	266	207										
418	266	208										
419	266	209										
420	266	210										
421	266	211										
422	266	212										
423	266	213										
424	266	214										
425	266	215										
426	266	216										
427	266	217										
428	266	218										
429	266	219										
430	266	220										
431	266	221										
432	266	222										
433	266	223										
434	266	224										
435	266	225										
436	266	226										
437	266	227										
438	266	228										
439	266	229										
440	266	230										
441	266	232										
442	266	233										
443	266	235										
444	266	236										
445	266	237										

N=35

Breast

Pharmacokinetic parameter estimates for PK/PD analysis (n=577 patients)

Study=232

OBS	Study	ID	CL/f (l/h)	CLu/f (l/h)	$\widehat{CL/f}$ (l/h)	$\widehat{CL/f}^*$ (l/h)	f1	f2	f3	f4	fu	AUC (ug/ml*h)
256	232	551										
257	232	552										
258	232	555										
259	232	556										
260	232	558										
261	232	559										
262	232	560										
263	232	561										
264	232	562										
265	232	563										
266	232	565										
267	232	566										
268	232	567										
269	232	568										
270	232	569										
271	232	570										
272	232	571										
273	232	572										
274	232	573										
275	232	574										
276	232	575										
277	232	577										
278	232	578										
279	232	581										
280	232	582										
281	232	583										
282	232	584										
283	232	587										
284	232	588										
285	232	590										
286	232	591										

N=31

NSCL

Pharmacokinetic parameter estimates for IDZIM analysis (n=577 patients)

Study=269

OBS	Study	ID	CLJ (l/h)	CLuJ (l/h)	$\widehat{CL}$J (l/h)	$\widehat{CL}$J* (l/h)	f1	f2	f3	f4	fu	AUC (ug/ml*h)
473	269	451										
474	269	452										
475	269	453										
476	269	455										
477	269	456										
478	269	457										
479	269	458										
480	269	459										
481	269	460										
482	269	461										
483	269	462										
484	269	463										
485	269	465										
486	269	466										
487	269	468										
488	269	469										
489	269	470										
490	269	471										
491	269	472										
492	269	473										
493	269	474										
494	269	475										
495	269	476										
496	269	477										
497	269	478										
498	269	479										
499	269	480										
500	269	481										
501	269	482										
502	269	483										
503	269	484										

N=31

NscL

Pharmacokinetic parameter estimates for IT/IP analysis (n=577 patients)

Study 270

OBS	Study	ID	CL1 (l/h)	CL2 (l/h)	CL1 (l/h)	CL1* (l/h)	f1	f2	f3	f4	fu	AUC (ug/ml*h)
504	270	751										
505	270	753										
506	270	754										
507	270	755										
508	270	756										
509	270	757										
510	270	758										
511	270	759										
512	270	760										
513	270	761										
514	270	762										
515	270	763										
516	270	765										
517	270	768										
518	270	769										
519	270	770										
520	270	773										
521	270	778										
522	270	780										
523	270	783										
524	270	784										
525	270	785										

N=22

NSCL

Pharmacokinetic parameter estimates for PE/IB analysis (n=577 patients)

Study=257

OBS	Study	ID	CLj (l/h)	CLuj (l/h)	$\widehat{CL}$j (l/h)	$\widehat{CL}$j* (l/h)	f1	f2	f3	f4	fu	AUC (ug/ml*h)
402	257	701										
403	257	702										
404	257	703										
405	257	706										
406	257	709										
407	257	710										
408	257	712										
409	257	713										
410	257	714										

N=9

Colorectal

Study=222

OBS	Study	ID	CLj (l/h)	CLuj (l/h)	$\widehat{CL}_j$ (l/h)	$\widehat{CL}_j^*$ (l/h)	f1	f2	f3	f4	fu	AUC (ug/ml*h)
59	222	1701										
60	222	1702										
61	222	1703										
62	222	1704										
63	222	1705										
64	222	1706										
65	222	1707										
66	222	1708										
67	222	1709										
68	222	1710										
69	222	1711										
70	222	1713										
71	222	1714										
72	222	1716										
73	222	1717										
74	222	1718										
75	222	1719										
76	222	1721										
77	222	1722										
78	222	1723										
79	222	1724										
80	222	1726										
81	222	1728										
82	222	1729										
83	222	1730										
84	222	1732										
85	222	1733										
86	222	1736										
87	222	1738										

N=29

Melanoma (N=29)
Mean CL = 34.8 L/hr
SD = 11.8 "

Pharmacokinetic parameter estimates for IT/IP analysis (n=577 patients)

Study=225

ONS	Study	ID	CL (l/h)	CLnl (l/h)	$\widehat{CL}$ (l/h)	$\widehat{CL}$* (l/h)	f1	f2	f3	f4	fu	AUC (ug/ml*h)
151	225	1603										
152	225	1604										
153	225	1605										
154	225	1606										
155	225	1607										
156	225	1608										
157	225	1609										
158	225	1611										
159	225	1612										
160	225	1614										
161	225	1618										
162	225	1619										
163	225	1620										
164	225	1621										
165	225	1622										
166	225	1623										
167	225	1624										
168	225	1626										
169	225	1627										
170	225	1629										
171	225	1630										

N=21

Renal (N=21)
Mean cl = 36.4 L/hr
SD = 15.5

Pharmacokinetic parameter estimates for PP/PD analysis (n=577 patients)

Study=236

OBS	Study	ID	CL (l/h)	CLnl (l/h)	$\hat{CL}$ (l/h)	$\hat{CL}^*$ (l/h)	f1	f2	f3	f4	fu	AUC (ug/ml*h)
318	236	1401										
319	236	1402										
320	236	1403										
321	236	1404										
322	236	1406										
323	236	1407										
324	236	1408										
325	236	1409										
326	236	1410										
327	236	1411										
328	236	1412										
329	236	1415										
330	236	1418										
331	236	1419										
332	236	1420										
333	236	1421										
334	236	1422										
335	236	1423										
336	236	1424										
337	236	1425										
338	236	1426										
339	236	1427										
340	236	1429										
341	236	1430										
342	236	1431										
343	236	1432										
344	236	1435										
345	236	1436										
346	236	1437										
347	236	1441										
348	236	1442										

N=31

Gastric (n=31)
Mean cl = 33.2 L/hr
SD = 9.8

Pharmacokinetic parameter estimates for PK/PD analysis (n=577 patients)

Study=252

OBS	Study	ID	CL/f (l/h)	CLd/f (l/h)	$\widehat{CL}/f$ (l/h)	$\widehat{CL}/f^*$ (l/h)	f1	f2	f3	f4	fu	AUC (ug/ml*h)
1	252	651										
2	252	653										
3	252	654										
4	252	655										
5	252	661										
6	252	662										
7	252	663										
8	252	664										
9	252	678										
10	252	684										

N=10

ovarian (n=10)

Mean cl = 41.7 L/hr

SD = 15.6 "

NOV 4 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

sNDA:	20-449/011 and 012
Submission Dates:	June 23, 1999 June 30, 1999
Drug Name:	Taxotere® (Docetaxel)
Formulation:	40 mg/ml Docetaxel (Anhydrous) in Single-Dose Vials For Intravenous Injection
Sponsor:	Rhone-Poulenc Rorer Pharmaceuticals Inc. Collegeville, PA
Reviewer:	Safaa Ibrahim, Ph.D.
Submission Type:	Review of an Efficacy Supplement

The sponsor submits a supplemental New Drug Application for the use of Taxotere® as a first- and second-line therapy in the treatment of patients with non-small cell lung cancer. The optimal dosing schedule for this patient population is 60-75 mg/m^2 administered as a one-hour intravenous infusion on day one of a twenty-one day cycle.

Docetaxel (Taxotere®) is a semisynthetic member of the taxoid family originally synthesized from

In the present application, the technical sections for Chemistry, Manufacturing and Controls, Preclinical Pharmacology and Toxicology, and Human Pharmacokinetics and Bioavailability were considered to be irrelevant to this efficacy supplement, and therefore, were not included in the submission. No changes have been made in the Clinical Pharmacology/Pharmacokinetics section of the current package insert for Taxotere®. However, the sponsor should address the following Comments:

COMMENTS

1. The sponsor is recommended to submit any pharmacokinetic information for docetaxel in patients with non-small cell lung cancer at the proposed dosing schedule of 60-75 mg/m^2.

2. The sponsor is also recommended to provide any information on the potential for drug-drug interactions between docetaxel and other drugs that are most commonly prescribed to patients with non-small cell lung cancer.

RECOMMENDATION

Please forward Comments 1 and 2 to the sponsor.

/S/ 11/4/99

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

/S/

Reviewer: Safaa Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

cc: sNDA 20-449
HFD-150/Division file
HFD-150/Statin, Beitz, Griebel
HFD-850/Lesko
HFD-860/Mehta, Rahman, Ibrahim
CDR (Biopharm)