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APPLICATION NUMBER:

202497Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

DATE	April 12, 2012
TO	Haleh Saber, PhD Pharmacology and Toxicology Supervisor Division of Hematology and Oncology Toxicology Office of Hematology and Oncology Products
FROM	M. Stacey Ricci, MEng, ScD Senior Toxicologist Division of Hematology and Oncology Toxicology Office of Hematology and Oncology Products
NDA	202497
SPONSOR	Talon Therapeutics, Inc.
PRODUCT	Marqibo® (vincristine sulfate liposome injection)
INDICATION	Philadelphia Chromosome-negative (Ph-) Adult Acute Lymphoblastic Leukemia (ALL) patients in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies
PDUFA DATE	May 12, 2012

BACKGROUND

This review is an addendum to the Pharmacology and Toxicology Review for the 505(b)(2) NDA application for Marqibo®. The original NDA application for Marqibo was submitted to FDA in 2003 under NDA 21600. The pharmacology and toxicology studies submitted to support the approval of NDA 21600 were also included in the current NDA, and these studies were reviewed by Dr. Doo Y. Lee Ham and archived in 2004.

A comparison of the study reports submitted in NDA 21600 that were reviewed by Dr. Lee Ham and the study reports submitted in NDA 202497 identified the following as being submitted only in NDA 202497:

Original Research:

1. Report 090423 - Effects of Vincritsine Sulfate and Marqibo on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells.
   - Laboratory: (b) (4)
   - Report Date: Jan. 15, 2010
   - GLP Compliant

Literature Reviews for Vincristine:

2. 4NC03R - Literature Summary of Antitumor Activity of Vincristine Sulfate in Mouse Tumor Models Employing Murine and Human Tumor Cell Lines

3. 4NC04R - Literature Summary of Nonclinical Safety Pharmacology Studies for Vincristine Sulfate
4. 4NC05R - Literature Summary of Nonclinical and Clinical Metabolism of Vincristine Sulfate
5. 4NC08R - Literature Summary of Nonclinical Pharmacokinetics for Vincristine Sulfate
6. 4NC07R - Literature Summary of Nonclinical and Clinical Drug-Drug Interactions for Vincristine Sulfate
7. 4NC06R - Literature Summary of Nonclinical General Toxicology Studies for Vincristine Sulfate
8. **4NC02R - Literature Summary of Genotoxicity Studies for Vincristine Sulfate**
9. **4NC09R - Literature Summary of the Carcinogenic Potential of the Active Ingredient (Vincristine) and Liposome Carrier Components of Vincristine Sulfate Liposomes Injection**
10. 4NC01R - Literature Summary of Reproductive Toxicity Studies for Vincristine Sulfate

Literature summaries were prepared by (b) (4) and are dated Nov. 12, 2010.

LABEL REVIEW

Talon Therapeutics included information in the proposed label about non-liposomal vincristine from the published literature and information about liposomal vincristine derived from their original research.

Label Information	Original Research	Published Research
Embryo-fetal toxicity	Study Report 1609-001*	-
Carcinogenicity	none	yes
Genotoxicity	none	yes
Impairment of Fertility	Study Report PN56852*	yes

** Reviewed by Dr. Lee Ham.*

The literature reviews about the carcinogenicity and genotoxicity of vincristine are summarized below. Also, data from the embryo-fetal toxicology study that are used to supported language in the labeling but were not included in Dr. Lee Ham's review are discussed below.

1. Report 4NC02R: Literature Summary of Genotoxicity Studies for Vincristine Sulfate

Prepared by: (b) (4)

Date: November 12, 2010

This review summarized published data for the genotoxicity and mutagenicity of non-liposomal vincristine sulfate to support registration for Marqibo. The review methodology included searching the scientific databases MEDLINE, ToxFile, NTIS and EMBASE using DialogLink software. Search terms used included but were not limited to:

- vincristine or 22-oxovincaleukoblastine or leurocristine or vincrystine or vinkristin
- genotox* or gene mutat* or clastogen* or Ames or Salmonella or chromosom* damage* or chromosom* aberrat* or micronucle*

The review filtered out only peer-reviewed full articles that described the doses of vincristine used and evaluated the study protocols with regard to ICH and OECD guidelines. The compiled results were summarized as follows in the review:

Test System	Number of Studies		
	Total	With Positive Results	With Negative Results
***In Vitro* Non-Mammalian**			
Bacterial Reverse Mutation	3	0	3
***In Vitro* Mammalian**			
Gross Chromosomal Damage: Chromosome Aberration	9	5	4
Gross Chromosomal Damage: Micronuclei	3	3	0
Gene Mutation	6	1	5
***In Vivo* Mammalian**			
Chromosome Aberration in Bone Marrow Cells	3	1	2
Erythrocyte Micronuclei Formation	12	12	0

Vincristine shows clear positive results for micronuclei formation using both in vitro and in vivo systems, which is consistent with its disruptive effects on microtubule formation. Results for the Ames assay (bacterial reverse mutation) were negative, as expected. The results for other endpoints were mixed. Therefore, the overall conclusion can be made that vincristine is genotoxic through clastogenic mechanisms related to its functional effects on chromosomal microtubule disruption.

2. Report 4NC09R: Literature Summary of the Carcinogenic Potential of the Active Ingredient (Vincristine) and Liposome Carrier Components of Vincristine Sulfate Carrier Components of Vincristine Sulfate Liposomes Injection

Prepared by: (b) (4)

(b) (4)

Date: November 12, 2010

This review summarized the published nonclinical and clinical literature relating to the carcinogenicity of vincristine sulfate, the epidemiology and tumorigenicity of related vincristine compounds and the potential tumorigenicity of sphingomyelin and cholesterol (the liposome carrier of Marqibo). The review methodology included searching several scientific databases, including MEDLINE, ToxFile, NTIS and EMBASE, using DialogLink software. Search terms used included but were not limited to:

- vincristine or 22-oxovincaleukoblastine or leurocristine or vincrystine or vinkristin
- vinblastine or vindesine or vinorelbine
- animal* or rat* or mouse or mice or dog* or rabbit* or pig* or guinea pig* or hamster* or monkey* or nonhuman primate* or non clinical or nonclinical or pre clinical or preclinical*
- clinical* or human* or subject* or patient* or volunteer* or man or men or male* or woman or women or female* or child* or infant* or juvenile* or teenager* or adolescent* or double blind or epidemiol* or cohort
- tumor* or carcino* or cancer* or neoplasm* or malignan* or oncogen* or oncol* or second* cancer* or second* tumor* or second* neoplasm* or second* malignan* or second* primary* cancer* or second* primary* tumor* or second* primary* neoplasm* or second* primary* malignan* or adenoma* or adenocarcinoma* or melanoma* or sarcoma*
- subchronic* or chronic* or long term* or repeat* dose* or 28 day or twenty eight day or 90 day or ninety day or life time

Terms that were used for searches pertaining to the potential toxicity of sphingomyelin and cholesterol included, but were not limited to, the following:

- sphingomyelin or cholesterol
- genotox* or mutat* or mutagen* or clastogen* or cytogen* or Ames or Salmonella or chromosom* damage* or chromosom* aberrant* or micronucle* or
- sister chromatid exchange*
- tumor* or carcino* or cancer* or neoplasm* or malignan* or oncogen* or oncol* or adenoma* or adenocarcinoma* or melanoma* or sarcoma

The review filtered out only peer-reviewed full articles that described the doses of vincristine used and evaluated the study protocols with regard to ICH and OECD guidelines.

There were no life-time carcinogenicity assays indentified using mice or rats that were considered consistent with GLP procedures. Nevertheless, the report

authors conclude that the data that are available from animal carcinogenicity studies using vincristine and other vinca alkaloids, and existing epidemiology data indicate that vincristine would not present a carcinogenic hazard under the conditions of its intended use in Marqibo. The authors also conclude that the sphingomyelin and cholesterol lipids used to formulate Marqibo do not pose any carcinogenic risk at therapeutic dose levels.

Species/Strain/Age, No. and Sex per Group	Dose/Duration, Route of Administration	Noteworthy Findings	Reference
Mouse/Swiss-Webster/6 weeks, 25 per sex	0.075 or 0.15 mg/kg bw/d (0.23 to 0.45 mg/m^2)/ 3 injections/week for 6 months (monitored for an additional 12 months), IP	No treatment-related effects on the incidence of neoplastic lesions at VCR doses of up to 0.45 mg/m^2. Treatment was associated with decreased survival in males.	Weisburger, 1977
Mouse/Swiss-Webster/6 weeks, 25 per sex/	0.005 to 0.5 mg/kg bw/d (0.02 to 1.5 mg/m^2)/ 3 injections/week for 6 months (monitored for an additional 12 months), IP (VCR was administered in combination with other agents)	No increase in singular tumor enhancement and no evidence of neoplastic development were noted. Combinations of VCR and cyclophosphamide resulted in higher tumor incidence than in controls, although results were attributed to cyclophosphamide.	Weisburger, 1977
Mouse/CBA/Ca/6 to 8 weeks, 12 per sex	0.025 to 0.036 mg/kg bw/d (0.08 to 0.11 mg/m^2)/ Daily for 12 months, route of administration NR (VCR was administered in combination with other agents).	Combinations of VCR and cyclophosphamide were associated with tumor formation and toxicity leading to death. Combinations of VCR in the absence of cyclophosphamide were not associated with tumor formation. No evidence of neoplastic development.	Ember *et al.*, 1995
Rat/Sprague-Dawley CD/6 weeks, 25 per sex	0.06 mg to 0.12 mg/kg bw/d (0.35 to 0.71 mg/m^2)/ 3 injections/week for 6 months (monitored for an additional 12 months), IP	No treatment-related effects on the incidence of neoplastic lesions at VCR at doses of up to 0.71 mg/m^2 compared to controls.	Weisburger, 1977
Rat/Sprague-Dawley CD/6 weeks, 25 per sex	0.0006 to 0.25 mg/kg bw/d (0.0036 to 1.48 mg/m^2)/3 injections/week for 6 months (monitored for an additional 12 months), IP (VCR was administered in combination with other agents)	No increase in singular tumor enhancement and no evidence of neoplastic development. Combinations of VCR and cyclophosphamide did result in higher tumor incidence than controls, which was attributed to cyclophosphamide.	Weisburger, 1977
Rat/Sprague-Dawley/ 100 d, 40 per sex	0.4 to 0.8 mg/m^2 (administered in combination with methotrexate and 5-fluorouracil; specific dose of VCR could not be calculated)/every 6 weeks for 6 or 18 cycles, IV	Administration of VCR combination was not associated with tumor development. Histopathological examination with treatment showed no effects.	Berger *et al.*, 1983

bw = body weight; d = day; F = female; IP = intraperitoneal; IV = intravenous; M = male; NR = not reported; PCV = packed cell volume; TVT = transmissible venereal tumor; VCR = vincristine; y = year.

The following is the FDA-proposed language for section 13.1 of the label regarding the carcinogenic potential of the drug:

No carcinogenicity studies have been conducted with Marqibo® or non-liposomal vincristine sulfate. Based on the mechanism of action and genotoxicity findings in nonclinical studies conducted with non-liposomal vincristine sulfate, Marqibo may be carcinogenic.

3. Study Report 1609-001: Intravenous Developmental Toxicity Study of Vincristine Sulfate Liposomes Injection, 0.16 mg/mL (VSLI) in Rats

Findings from the developmental toxicology study conducted using vincristine sulfate liposome injection (VSLI) were reviewed previously by Dr. Lee Ham, but the following information is included below to provide support for comparative rat: human exposure of VSLI to support information to be included in labeling for Marqibo:

Vincristine sulfate (VSI) or VSLI were administered at amounts resulting in equivalent doses of vincristine (see table below containing Dosage information; table copied from p. 1-1 of Study Report 1609-001).

Group	Test Material Identification	Dosage[a]		Number of rats[b]	Concentration (mg/mL)	Dosage Volume (mL/kg)[c]
		(mg/m^2/day)	(mg/kg/day)			
I	Saline	0	0	25	0	2.81
II	Empty Liposome[d]	0	0	25	0	2.81
III	VSI	0.30	0.044	25 + 18	0.032	1.38
IV		0.45	0.066	25 + 18	0.032	2.06
V		0.60	0.090	25 + 18	0.032	2.81
VI	VSLI	0.15	0.022	25 + 18	0.032	0.69
VII		0.30	0.044	25 + 18	0.032	1.38
VIII		0.45	0.066	25 + 18	0.032	2.07
IX		0.60	0.090	25 + 18	0.032	2.81

a. Dosages are in terms of vincristine levels. Conversions of dosages between units of mg/m^2 and mg/kg/bw are based on a 225 g rat, with a body surface area (BSA) of $0.0337m^2$ using the formula: $SA = (bw \text{ in grams})^{0.66} \times K/10^4$, where K = 9.1.

b. Eighteen rats assigned to toxicokinetic evaluation.

c. Dosage volumes were adjusted daily on the basis of the individual body weights recorded before injection.

d. Dosages of Empty Liposomes are equivalent to the liposome content of the high dose of VSLI.

Toxicokinetic Results

Mean plasma concentrations of vincristine on Days 7 and 17 for groups treated with VSLI were much greater than plasma concentrations for similar dosages of VSI (below table was copied from page 1-3 of the study report). The value for AUC_{last} on Day 17 for VSLI were 100- to 200-fold greater than the AUC_{last} for VSI at equivalent VSI doses.

Summary of AUC_{max}, AUC and C_{max} values

Group	AUC_{last} (ng·h/mL)		AUC (ng·h/mL)		C_{max} (ng/mL)	
	Day 7	Day 17	Day 7	Day 17	Day 7	Day 17
VSI Administration						
III (0.044 mg/kg/day)	0.218	29.3	NE	59.5	5.24	7.77
IV (0.066 mg/kg/day)	5.72	50.9	NE	60.2	8.77	47.4
V (0.090 mg/kg/day)	11.9	19.6	NE	NE	8.81	16.4
VSLI Administration						
VI (0.022 mg/kg/day)	94.2	255	NE	NE	169	452
VII (0.044 mg/kg/day)	2280	5590	2610	5600	458	911
VIII (0.066 mg/kg/day)	8180	12600	8180	12800	903	1120
IX (0.090 mg/kg/day)	8350	14600	8390	15600	1280	1160

NE: Not Estimated; terminal phase was not characterized.

Developmental Effects

The effects of VSLI and VSI were tabulated in the Study Report and shown below (copied from p. 1-6). There were no adverse effects in dams that received 0.022 mg/kg/day of VSLI or the empty liposome on the developmental parameters measured when compared to saline control.

Summary of Developmental Observations at 0.044, 0.066 and 0.090 mg/kg/day Dosages of Vincristine Sulfate and VSLI

		0.044 mg/kg/day	0.066 mg/kg/day	0.090 mg/kg/day
Early resorptions (No./dam)	VSI	0.8	1.8*	11.3**
	VSLI	1.4	4.8**	13.0**
Late resorptions (No./dam)	VSI	0.0	0.8**	1.0*
	VSLI	0.2	0.5	0.8*
% dams with resorptions	VSI	68.0*	83.3**	100**
	VSLI	68.0*	95.4**	100**
% dead or resorbed/litter	VSI	5.0	17.0**	74.0**
	VSLI	7.1	32.4**	76.8**
fetal body weights (Grams)	VSI	5.13	4.70**	3.82**
	VSLI	5.23	4.42**	3.35**
% litters with fetuses with alterations	VSI	84.0**	100**	100**
	VSLI	62.5*	100**	100**
% fetuses with alterations.	VSI	15.7**	54.2**	97.9**
	VSLI	12.2**	60.7**	90.2**
% fetuses with alterations/ litter	VSI	15.7**	56.8**	98.9**
	VSLI	11.9	68.8**	96.1**

VSI = Vincristine Sulfate, VSLI = Vincristine Sulfate Liposomes Injection

* significantly different from saline control ($p \leq 0.05$)

** significantly different from saline control ($p \leq 0.01$)

The litter averages for corpora lutea, implantations and placental weights were unaffected by doses of VSLI up to and including 0.09 mg/kg/day. All placenta appeared normal.

Comparison with estimated human exposure at clinical dose

The plasma pharmacokinetic analysis was investigated in 13 adult patients with relapsed ALL who received a dose of 2.25 mg/m^2 administered as a 1 hour intravenous infusion.

Variable	N	Mean	SE	Median	Range
AUC_∞ (h•ng/mL)	13	14566	1766	13680	7036-26074
CL (mL/h/m^2)	12	345	100	302	148-783
C_{max} (ng/mL)	13	1220	64	1230	919-1720

[a] Dose was administered as a 1 hour infusion.

The following table compares systemic human VSLI exposures to systemic exposure of VSLI in pregnant rats:

Species	Dose	C_{max} (ng/ml)	AUC_∞ (h•ng/mL)	Animal:human exposure	
				C_{max}	AUC
Human	2.25 mg/m^2	1220	14566	-	-
Rat Day 7	0.022 mg/kg	169	NE	0.138525	-
	0.044 mg/kg	458	2610	0.37541	0.179184
	0.066 mg/kg	903	8180	0.740164	0.561582
	0.090 mg/kg	1280	8390	1.04918	0.575999
Rat Day 17	0.022 mg/kg	452	NE	0.370492	-
	0.044 mg/kg	911	5600	0.746721	0.384457
	0.066 mg/kg	1120	12800	0.918033	0.878759
	0.090 mg/kg	1160	15600	0.95082	1.070987

Fetal malformations occurred at doses ≥ 0.044 mg/kg/day in pregnant rats. Based on the systemic exposure to VSLI observed in rats at a dose of 0.044 mg/kg/day, the equivalent systemic exposure is equivalent to 17.9% to 38.4% of the recommended human dose of Marqibo (2.25 mg/m^2). This comparison supports including the following statement for labeling:

"Malformations were observed at doses ≥ 0.044 mg/kg/day in animals at systemic exposures approximately 20-40% of those reported in patients at the recommended dose."

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/s/

M S RICCI
04/12/2012

HALEH SABER
04/12/2012

MEMORANDUM

Date: March 30, 2012
From: Haleh Saber, Ph.D.
Pharmacology/Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
NDA: 202497
Drug: Marqibo® (vincristine liposome injection)
Indication: Philadelphia Chromosome-negative (Ph-) Adult Acute Lymphoblastic Leukemia (ALL) patients in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies

Marqibo® is a liposomal encapsulated vincristine. This is a 505 (b)(2) NDA application, relying on the data from Vincristine Sulfate Injection as presented in the label for this drug or on published literature to address certain nonclinical sections of the label. Vincristine, a vinca alkaloid, is an approved drug for treatment of acute leukemia. In general, liposomal formulation of a drug may result in reduced C_{max}-related toxicities and increased AUC-related toxicities. The Applicant suggests that the encapsulated formulation will reduce vincristine-related neurotoxicities.

The original NDA application for Marqibo was submitted to the FDA in 2003, under NDA # 21600. The nonclinical studies were reviewed by Dr. Doo Y Lee Ham. No nonclinical approvability issues were identified by the reviewer; the review was archived on 3/15/2004. According to the review, the liposomal vincristine (VSLI) had a better anticancer activity in the murine tumor models when compared to the free vincristine (VCR). However, repeat-dose toxicology studies in rodents suggest increased neurotoxicity associated with VSLI when compared to VCR. In a 6-cycle repeat-dose toxicology study in Sprague-Dawley rats, VSLI or VCR was administered to animals intravenously once per week. Clinical signs of toxicity suggestive of neurotoxicity were more evident with VSLI than with VCR at equal doses of 2 mg/m^2/week and included uncoordinated movements, weakness/ reduced muscle tone, and limited usage of the limbs. Neurological testing using a standard Functional Observation Battery after six cycles of VSLI or VCR at 2 mg/ m^2/week indicated that both VSLI and VCR induced peripheral neurotoxicity. Based on the histopathology examination after 6 cycles of VSLI or VCR dosing, VSLI induced greater peripheral neurotoxicity (nerve fiber degeneration) and secondary skeletal muscle atrophy than the equal dose of VCR. In a separate tissue distribution study in rats, 2 mg/m^2 of VSLI or VCR was administered to animals. Significantly greater (2 to 3-fold) accumulation of vincristine was observed in sciatic and tibial nerves of the animals after administration of VSLI. Based on the findings in animals, the increased anticancer activity of the liposomal vincristine was accompanied by increased peripheral neuropathy.

Other drug-related toxicities included hematologic, hepato-, GI, and dental toxicities, and toxicities to the male reproductive organs. In general, drug-related neurotoxicity was the (dose-limiting toxicity) DLT in rodents while hematologic toxicities were the DLTs in the non-rodent species. VSLI caused embryofetal toxicities in animals, including teratogenicity, similar to what was previously reported with free vincristine. No genotoxicity studies have been conducted with VSLI. The free vincristine was genotoxic in some *in vitro* and *in vivo* studies.

The Applicant conducted pharmacology studies with the liposomal and free vincristine, supplemented with published literature on free vincristine. Pharmacokinetic, distribution, mass balance, and metabolism studies were conducted with VSLI; literature was also provided, e.g. on excretion of free vincristine. Some PK/ADME studies conducted by the Applicant were comparative studies (VSLI versus VCR). Repeat-dose toxicology studies were conducted in rats (6 weeks) and dogs (23 weeks). An embryo-fetal developmental study of VSLI was conducted in rats. The Applicant relied on published literature on free vincristine for the assessment of genetic toxicity (section 13.1 of the label). In studies conducted by the Applicant, the route of administration in animals was I.V., consistent with the proposed route of administration in patients. In addition to literature references reviewed during the first review cycle, references have been submitted by the Applicant to the current NDA and reviewed by Dr. Stacey Ricci.

Two nonclinical issues were raised by Dr. Lee Ham in 2004; see below the reviewer's comments. These were recommendations, not approvability issues.

- "The PK data for VSLI and VCR suggest that encapsulation of vincristine in liposomes increases the longevity of the drug in the plasma compartment. Moreover, "free" vincristine released from VSLI declined in a biexponential manner, with concentrations from 7 to 4 ng eq/mL over 4-120 h post-dosing. This plasma concentration represents a small fraction (%) of the administered dose of vincristine in VSLI, which is a lower exposure to free VCR than when non-liposomal VCR is administered. The sponsor needs to provide adequate supporting evidence that the reduced exposure to free vincristine versus exposure following dosing with VCR does not represent sub-therapeutic dosing of vincristine.
- The tissue distribution data indicates that Cmax and AUC of total vincristine in some tissues of VSLI-treated animals were higher than after VCR administration. These data suggest that greater accumulation and potentially higher exposure of the tissues were attained after VSLI dose. However, no data are available to assess the bioavailability of vincristine in tissues after VSLI injection. The sponsor needs to provide information regarding the extent of released vincristine in tissues after VSLI administration."

The first comment is no longer relevant as the clinical dose of the drug has been identified based on clinical studies conducted to date. The second comment is not applicable anymore; the recommended data are not required based on ICH S9 Guidance.

Recommendation: Marqibo may be approved for the proposed indication. No additional nonclinical studies are needed to support approval of Marqibo for the proposed indication.

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/s/

HALEH SABER
03/30/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202497 **Applicant:** Talon **Stamp Date:** July 13, 2011

Drug Name: Marqibo (vincristine sulfate liposomes injection) **NDA Type:** Original

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		x	Will communicate with the applicant and request revisions.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			Will be a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?		x	N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		x	N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

YANLI OUYANG
09/01/2011

HALEH SABER
09/02/2011