

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204308Orig1s000

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204308 Applicant: (b)(4)

Stamp Date: 08-10-2012

Drug Name: Enalapril maleate NDA/BLA Type: 505(b)2

[14.3% enalapril maleate powder for oral solution for treatment of (b)(4) hypertension]

On **initial** overview of the NDA/BLA 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		(b)(4) references to the nonclinical section of the Vasotec label (the reference listed drug) to fulfill the nonclinical requirements for the 505(b)(2) NDA.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		(b)(4) references to the nonclinical section of the Vasotec label (the reference listed drug) to fulfill the nonclinical requirements for the 505(b)(2) NDA. In supplement, (b)(4) added 6 literature references pertaining to the use of enalapril maleate in juvenile animals.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		In addition to the Monograph 2010 for Vasotec, the pharmacology and toxicology review will be limited to 6 "updated" literature references using juvenile animals to support a pediatric indication.
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		(b)(4) references to the nonclinical section of the Vasotec label (the reference listed drug) to fulfill the nonclinical requirements for the 505(b)(2) NDA.
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	The Sponsor is developing a formulation of (b)(4) enalapril maleate powder for oral solution for treatment of (b)(4) hypertension. The sponsor is submitting a 505(b)(2) NDA by referencing Vasotec tablets (NDA 018998 held by Biovail Labs, International) and the possibility of an orphan drug designation. All pharmacology and toxicology studies referenced to Vasotec and sponsor seeks approval based on the Agency's finding of safety and/or effectiveness for Vasotec.

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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 <u>submitted</u> a rationale to justify the alternative route?	X		All pharmacology and toxicology studies referenced to Vasotec and sponsor seeks approval based on the Agency's finding of safety and/or effectiveness for Vasotec.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		Sponsor seeks approval based on the Agency's finding of safety and/or effectiveness for Vasotec.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		No supplementary pharmacology and toxicology studies were required during the Pre-IND meeting with sponsor that took place on October 1, 2010.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		No new labeling sections were provided by sponsor regarding pharmacology and toxicology. The proposed draft labeling will be almost identical to the approved labeling for Vasotec tablets. Differences will be the inclusion of the bioavailability study results, deletion of directions for the preparation of a suspension using tablets, and revisions to the "How Supplied" section and manufacturing and distribution contact information.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		The formulation for (b) (4) (Enalapril Maleate USP) Powder for Oral Solution for (b) (4) indication is a dry blend of enalapril maleate, mannitol, and colloidal silicon dioxide (b) (4). There are no new related substances generated in the drug product that are not known to exist in the API. All related substances/impurities are the same as those reported in the drug substance, namely (b) (4)
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _____ X _____

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

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

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.

Muriel Saulnier	08-30-2012
_____ Reviewing Pharmacologist	_____ Date

_____ Team Leader/Supervisor	_____ Date
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MURIEL J SAULNIER
09/07/2012

ALBERT F DEFELICE
09/07/2012