CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-540

PHARMACOLOGY REVIEW(S)

NDA 21540 Caduet (amlodipine besylate/atorvastatin calcium) Tablets Pfizer Inc.

SUPERVISORY PHARMACOLOGIST'S REVIEW OF LABELING[9]

C.A. Resnick, Ph.D.
DCRDP (HFD-110)

This application is for several fixed combinations of amlodipine besylate and atorvastatin calcium. Both are approved drugs. The besylate salt of amlodipine, a calcium channel blocker, is marketed by Pfizer as Norvasc® and is approved for use in the treatment of hypertension and angina (NDA 19787). The calcium salt of atorvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, also marketed by Pfizer, as Lipitor®, is approved for use in the treatment of dyslipidemia (NDA 20702). Approval is being sought for 8 fixed combinations of these drugs (5/10, 5/20, 5/80, 10/10, 10/20, 10/40, and 10/80 mg amlodipine/atorvastatin) for use in patients for whom the individual drugs are currently approved. Nonclinical pharm/tox studies on the combination of amlodipine besylate and atorvastatin have not been carried out and the sponsor is relying on data contained in their NDAs for Norvasc® and Lipitor® as documentation of the safety of the individual drugs. In view of the above, and in recognition that clinical trial data will address potential pharmacodynamic and pharmacokinetic interactions of amlodipine with atorvastatin, a formal pharmacology/toxicology review of this application is not needed.

Regarding those sections of labeling that deal with nonclinical evaluations of the toxicity of amlodipine and atorvastatin, the proposed labeling for this combination product contains the same information as provided by the package inserts for Norvasc® and Lipitor®, and that information is considered adequate for the Caduet insert.

Some minor changes are, however, recommended and these are presented below. It should be noted that the recommended revisions are limited to statements dealing with the amlodipine component of the combination and these recommendations also apply to the sponsor's other amlodipine product, Norvasc®. The recommendations are made in the interest of clarity, in most cases to identify the administered drug as amlodipine maleate and to make clear that all doses are expressed in terms of the amlodipine base. The sponsor should consider similar changes for the statements dealing with atorvastatin (i.e. make clear that in animals atorvastatin calcium was administered and that all doses are expressed in terms of atorvastatin base).

*Under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**, the first paragraph should be changed from:*

---

[9] Version of labeling reviewed is version included with original application (CDER receipt date 01 April 2003)

Number of Pages Redacted 2

❖❖❖

Draft Labeling
(not releasable,

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Charles Resnick .
9/9/03 09:47:39 AM
PHARMACOLOGIST

NDA 21-540 CADUET™ (amlodipine besylate/atorvastatin calcium) Tablets Pfizer Inc.

Original Amendment dated 11 August 2003

REVIEW OF NONCLINICAL INFORMATION REGARDING TOXICOLOGY STUDIES OF AMLODIPINE

C.A. Resnick, Ph.D.
DCRDP (HFD-110)

The current amendment was submitted in response to a request made of Pfizer by this reviewer (phone call to Natalie Touzell on 16 July 2003). I had asked that the Division be provided with the identity of the salt of amlodipine (besylate or maleate) that was employed in each of the laboratory animal studies referred to in the proposed labeling for CADUET™ . Note that statements regarding amlodipine in the proposed CADUET™ labeling were taken directly from the approved labeling for Norvasc (amlodipine besylate) tablets.

According to the attached listing (provided by the sponsor), studies were conducted with both the besylate and maleate salts. However, by comparing study numbers provided by the sponsor with the study numbers provided in the original pharm/tox review for Norvasc (reviewer had provided study numbers but had not identified the salt employed) we are able to conclude that the maleate studies were the studies that provided the information that appears in the package insert for Norvasc under "Carcinogenesis, Mutagenesis, Impairment of Fertility" and "Pregnancy".

Salt Identification for Norvasc and Caduet Labeling.doc
August 28, 2003

Norvasc NDA Studies

Carcinogencity Studies	Salt Administered
#84089 24 month Oral (Dietary admix) Carcinogencity Study in Mice	maleate
#84088 24 month Oral (Dietary admix) Carcinogencity Study in Rats	maleate
Reproduction Studies	
#84010 Fertility Study in Rats by the Oral Route (Segment I and II)	maleate
#86-48-41 Abstract: segment Study of Amlodipine Besylate in Rats	besylate
#83074 Foetotoxicity Study in Rats by the Oral Route (Segment II)	maleate
#86-48-54 Abstract: Segment II Study of Amlodipine Besylate in Rats	besylate
#85004 Foetotoxicity Study in Rabbits by the Oral Route (Segment II)	maleate
#86-48-61 Abstract: Segment II Study of Amlodipine Besylate in Rats	besylate
Mutagenicity Studies	
Genetic Toxicology Report and Addendum	maleate
#86-48-81 and 86-48-82 Abstract: Genetic Toxicity Study of Amlodipine besylate	besylate
Overdosage Section/Acute Toxicity	
# 82129 / 82130 / 82131 / 82132 Acute Oral and Intraveneous Toxicity Studies in Rodents	maleate
#85-48-02 An Acute Oral Toxicity Study with Amlodipine besylate in Rats	besylate
#87022 Acute Oral Toxicity Study in Male Dogs (oesophageal intubation)	maleate