CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20943

CHEMISTRY REVIEW(S)

NOV -1 6 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-943 DATE REVIEWED: August 10, 1998
CHEMISTRY REVIEW #: 1 REVIEWER: Kathleen E. Jongedyk

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED	RECEIVED
ORIGINAL	23-Dec-97	30-Dec-97	05-Jan-98	08-Jan-98
AMENDMENT	20-Mar-98	24-Mar-98	25-Mar-98	27-Mar-98
AMENDMENT	12-May-98	14-May-98	18-May-98	19-May-98

NAME & ADDRESS OF APPLICANT: Elan Pharmaceutical Corporation
1300 Gould Drive
Gainesville, Georgia 30504

DRUG PRODUCT NAME
Proprietary: Circelan
Nonproprietary/Established/USAN: Verapamil Hydrochloride
Code Name/#: CAS: 152-11-4
Chem.Type/Ther.Class: S

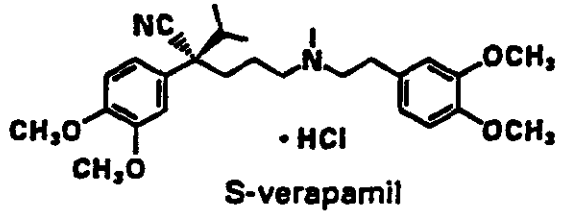
PHARMACOLOGICAL CATEGORY/INDICATION:
Inhibits Calcium Ion Influx Essential Hypertension

DOSAGE FORM: Capsules
STRENGTHS: 100 mg, 200 mg, 300 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx ___ OTC
CLASSIFICATION: S

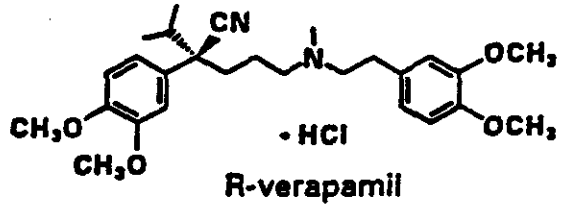
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Molecular Weight	Molecular Formula
491.07	$C_{27}H_{38}N_2O_4 \cdot HCl$

(1) Benzeneacetonitrile, a-[3-[[2-(3,4- dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-a-(1-methylethyl)-, monohydrochloride, (+)
(2) (+)-5-[(3,4-Dimethyoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile, monohydrochloride



S-verapamil



R-verapamil

SUPPORTING DOCUMENTS:

DMFType#	Subject	Holder	Status	Review	Letter
	Drug Substance		acceptable	30-Jul-98	---
	Plastic Bottles		acceptable		
	resin		acceptable	04-Dec-997	---
	Plastic Bottles		acceptable	25-Aug-98	---
	Plastic bottles			31-Jul-98	03-Aug-98
	Closures		Type 1	Review not	required
	Closure resin		acceptable	03-Dec-97	---
	Inner seal		acceptable	03-Sep-98	---
	Closures		acceptable	03-Apri-98	---
	Closure resin		acceptable		update 14-May-98 07-Aug-98
	Closure resin		acceptable	28-Jan-98	---
	Closure resin		acceptable	27-Jun-95 29-Jul-98	---
	Closure resin		acceptable	26-Mar-98	---
	Closure resin		acceptable	02-Dec-97	---
	Closure		acceptable	30-Oct-97	---
	Closure resin		acceptable	24-Jan-97	---

	Closure resin		acceptable	18-Sept-98	---
	Closure liner		acceptable	30-Sept-97	
	Foils for blisters		deficient Response Acceptable	1-Mar-98 23-Mar-98	13-Mar-98 ----
	Film Laminate			20-Sept-98	24-Sept-98
	Lining material		acceptable	31-Jul-98	---
	Capsules		--	Oct-97	31-Oct-97

RELATED DOCUMENTS (if applicable):

NDA 19-614 **Verelan SR (verapamil hydrochloride) Capsules Elan**
Elan Pharmaceutical Research Corporation

IND **Verapamil PM (verapamil hydrochloride) Capsules Elan**

CONSULTS: Division of Biopharmaceutics

REMARKS:

March 20, 1998 amendment provides for revised manufacturing control document. Corrections, namely, revisions made for 300 and more deviations in these records found by the FDA investigator and afterwards additional deviations found by Elan in their internal audit.

May 12, 1998 amendment provides for revised labeling. See LABELING revisions requested.

Vol. 1, pp 32, 95, LOA 19-Dec-97 Elan references the manufacturing control information in 19-614 to 20-943. Specific topics with the date and page numbers where this information can be found can be cross referenced but the referencing the entire NDA 19-614 (submitted 1987) is too vague.

Elan cross references 20-943 provisions to 19-614 thus requesting approval for both NDAs. This is not acceptable and would make it difficult if not impossible to follow each NDA. Information provided and approved in NDA 20-943 is not approved for NDA 19-614. NDA 20-943 revised timed beads manufacturing process is significantly changed from NDA 19-614 timed bead manufacturing process.

Redacted 3

pages of trade

secret and/or

confidential

commercial

information

CONCLUSIONS & RECOMMENDATIONS: The NDA is approvable from the standpoint of CMC

cc:
Org. NDA 20-943
HFD-110/Division File
HFD-810/Kjongedyk
HFD-110/Project Manager
HFD-810/
HFD-810/Hoiberg Director
R/D Init by: 20943.JUL
20943.S81 August 6, 1998

/S/

Kathleen E. Jongedyk, Chemist 20943.1BK

/S/ 10-30-98

KOEDER

NOV 16 1998

DIVISION OF CARDIO RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-943 **DATE REVIEWED:** 14-Oct- 1998

REVIEW #: 2 **REVIEWER:** Kathleen E. Jongedyk

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	RECEIVED DATE
ORIGINAL	23-Dec-97	30-Dec-97	05-Jan-98	
AMENDMENT	28-Aug-98	31-Aug-98	09-Sept- 98	
	31-Aug-98	01-Sept-98	09-Sept-98	
	29-Sept-98	30-Sept-98		
	08-Oct-98	08-Oct-98	14 - Oct - 98	
	15 -Oct-98	16 -Oct-98	16 - Oct - 98	

NAME & ADDRESS OF APPLICANT:

Elan Pharmaceutical Research Corporation
1300 Gould Drive,
Gainesville, Georgia 300504

DRUG PRODUCT NAME

Proprietary:	Circelan
Established:	Verapamil Hydrochloride
Code Name/#:	CAS 152-11-4
Chem.Type/Ther.Class:	S

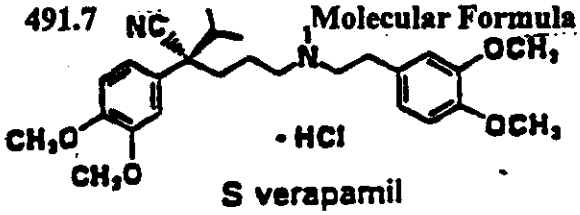
PHARMACOL. CATEGORY/INDICATION: Treatment of essential hypertension
Calcium channel blocker

DOSAGE FORM: Capsule
STRENGTHS: 100 mg, 200 mg, 300 mg

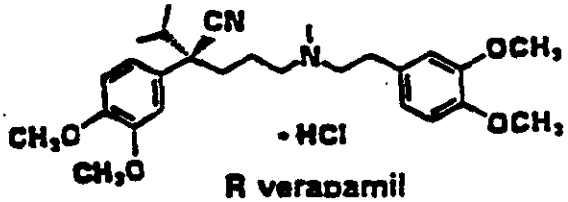
ROUTE OF ADMINISTRATION: Oral
Rex/OTC: X Rex ___ OTC
SPECIAL PRODUCTS: ___Yes X No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMLA AND WEIGHT:

Molecular Weight 491.7 **Molecular Formula** $C_{27}H_{38}N_2O_4 \cdot HCl$



S verapamil



R verapamil

SUPPORTING DOCUMENTS: See Chemist Review #1

29-Sept-98 amendment

Elan deleted the suppliers Drug Plastics for plastic bottles, Rexam for closures, and Phillip Sumkia for closures resin.

Type/Number	Subject	Holder	Status	Review Date	Letter Date
Revised	29-Sept-98				
	Verapamil HCl		Acceptable	07-Oct-98	—
	Plastic bottles		Acceptable		
	resin		Acceptable		
	Plastic bottles		Acceptable		
	inner seal		Acceptable		
	Closure		Acceptable		
	Closure resin		Acceptable		
	Closure resin		Acceptable		
	Closure resin		Acceptable		
	Closure resin		Acceptable		
	Closure resin		Acceptable		
	Closure		Acceptable		
	Closure resin		Acceptable		
	Closure resin		Acceptable		
	Closure resin		Acceptable		
	Foil for blister		Acceptable		
	Film laminate		Acceptable		

RELATED DOCUMENTS (if applicable): See Chemist Review #1

CONSULTS: Division of Biopharmaceuticals

REMARKS:

CONCLUSIONS AND RECOMMEDNATIONS:
Elan is submitting additional information therefore no conclusions and recommendations will be provided at this time.

cc:
Orig. NDA 20-943
HFD-110/Division File
HFD-810/KJongedyk
HFD-110/Project Manager
HFD-CHoiberg Director
R/D by: KSrinivasachara
Filename 20943.S81

/S/
Kathleen E. Jongedyk, Chemist

/S/
11-13-98

NOV 16 1998

DIVISION OF CARDIO RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-943 **DATE REVIEWED:** 23-Oct- 1998

REVIEW #: 3 **REVIEWER:** Kathleen E. Jongedyk

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE RECEIVED DATE
ORIGINAL	23-Dec-97	30-Dec-97	05-Jan-98
AMENDMENT	15-Oct-98	16-0ct-98	22-Oct-98
	16-Oct-98	19-Oct-98	22-Oct-98
	22-Oct-98	23-Oct-98	23-Oct-98

NAME & ADDRESS OF APPLICANT: Elan Pharmaceutical Research Corporation
1300 Gould Drive,
Gainesville, Georgia 300504

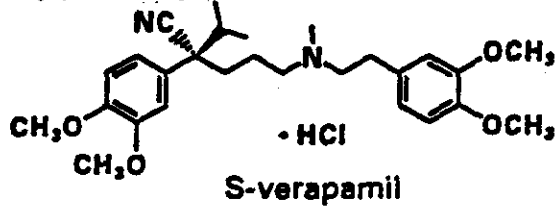
DRUG PRODUCT NAME

Proprietary:	Circelan
Established:	Verapamil Hydrochloride
Code Name/#:	CAS 152-11-4
Chem.Type/Ther.Class:	S

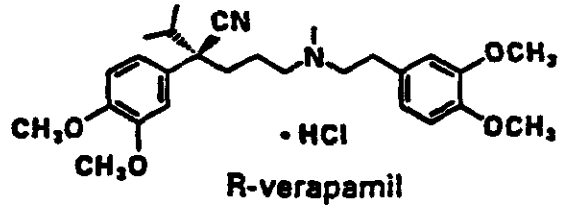
PHARMACOLOGICAL CATEGORY/INDICATION:
Channel Calcium Blocker Treatment of Essential Hypertension

DOSAGE FORM:	Capsule
STRENGTHS:	100 mg, 200 mg, 300 mg
ROUTE OF ADMINISTRATION:	Oral
Rx/OTC:	X Rx __ OTC
SPECIAL PRODUCTS:	__Yes X No

CHEMICAL NAME, STRUCTURAL FORMULA
Molecular Weight 491.07 **Molecular Formula** $C_{27}H_{38}N_2O_4$. HCl
Benzeneacetonitrile, a - [3-[[2- (3,4-dimethyoxyphenyl)ethyl] methylamino]propyl]-3,4-dimethoxy-a-(1-methylethyl), monohydrochloride (±)



S-verapamil



R-verapamil

SUPPORTING DOCUMENTS: See Chemist Reviews #1 and #3.
RELATED DOCUMENTS (if applicable): See Chemist Review #1
CONSULTS: Division of Biopharmaceuticals

REMARKS:

The following requests should be included in the approvable letter:

1- A supplemental application is required to be submitted for approval of the provisions in NDA 20-943 for another application; e.g., NDA 19-614.

2- An 18 month expiration date for the drug product is recommend based on twelve month acceptable stability data when stored at 25°C/60%RH and with failures reported when stored at 40°C/75%RH.

3- Please consider using the following storage statement in the "How Supplied" section of the package insert and in the container labels as provided in the draft Guidance for Industry Stability testing of drug substances and drug products, November 25, 1997:

"Store at 25°C(77°F); excursions permitted to 15-30°C(59-86°F)
[see USP Controlled Room Temperature]"

Where space on the immediate container is limited either of the following statements is acceptable, provided the full labeling statement, as shown above, appears on the outer carton and in the package insert:

"Store at 25° C (77° F); excursions 15-30°C (59-86°F)"

OR

"Store at 25° C (77° F) (see insert)"

4- The statement that FDA expects the applicant to cooperate with the Agency in the method validation for NDA 20-943.

Request revision of labels and labeling upon resolution of issues discussed in the Drug Product review LABELING section for Review 1, 2, 3 , such as the use of:

(1) the words "CONTROLLED ONSET"
(2) the words "ONCE DAILY AT BED TIME"
(3) the word "CODAS™ (Chronotherapeutic Oral Drug Absorption System) technology

CONCLUSIONS AND RECOMMEDATIONS:

NDA 20-943 is approvable from the standpoint of chemistry, manufacturing, and controls with the informational requests as outlined in the Remarks section included in the letter and resolution of the labeling revisions as outline in the Remarks section. Additional discussion is provided in Review 1, 2, 3 Drug Product Review Labeling.

CC:
Orig. NDA 20-943
HFD-110 Division File
HFD-810 KJongedyk 23/Oct/98
HFD-810/Kasturi Srinivasachar
HFD -110/ CSO
HFD- 810/ CHoiberg/Director of ONDC
R/D Init. by: Team Leader Kasturi Srinivasachar

/S/
Review Chemist

Filename: 20943REV#3.2310. doc

/S/
11-16-98