CHEM

D.R.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW

NDA 19-746 Date Completed: December 14, 1990

A. 1. Applicant: Sandoz Pharmaceuticals Corp.
Route 10
East Hanover, NJ 07936
(Douglas W. Bliss 201-503-8604)

ANDA: 19-463

2. Product Name (s): DYNACIRC (isradipine) CAPSULES

Proprietary: Dynacirc

Nonproprietary: Isradipine

USAN: Isradipine

Compendium: Not yet assigned.

International Nonproprietary (INN, WHO): Isradipine

Code Name and/or Number: PN 200-110 n
AW 200-110 n
200-110 n
200-110 base
200-110 b
PN 200-110
CAS-75695-93-1

Patent Information: US Patent 4,446,972 expires August 21, 2001

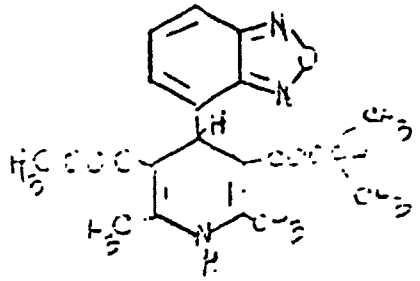
3. Dosage Form and Route of Administration:

2.5 mg, 5.0 mg, 7.5 mg, and 10 mg capsules for oral administration, Rx.

4. Pharmacological Category and/or Principal Indications:

Antihypertensive.

5. Structural Formula and Chemical Name:



Chemical Name (s):

3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl, methyl 1-methylethyl ester

Isopropyl 4-(2,1,3-benzoxadiazol-4-yl,-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylate

4-(2,1,3-Benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid, 3-methyl-5-(1-methylethyl)ester

3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl,-1,4-dihydro-2,6-dimethyl-, 3-methyl-5-(1-methylethyl)ester

Isopropyl methyl 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

4-(4-Benzofurazanyl -1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid, 3-methyl-5-(1-methylethyl)ester

Molecular Formula: $C_{19}H_{21}N_3O_5$

Molecular Weight: 371.39

MP: 166.0-170.0°C

B. 1. Initial Submission:

Date Submitted: December 27, 1985

Date Received: December 27, 1985

Date to Chemist: January 21, 1986

2. Amendments:

May 30, 1986	Summaries and labeling.
November 16, 1986	Chemistry, manufacturing and controls information.
October 24, 1986	Response to deficiencies.
July 20, 1987	Response to deficiencies in methods validation.
December 17, 1987	Change in branding for all strengths.
November 22, 1988	Safety update and draft labeling.
December 21, 1988	Response to information request.
November 17, 1989	Draft labeling for physician and pharmacy sample packages.
May 11, 1990	Revision in DESCRIPTION section of package insert.
November 28, 1990	Revised draft labeling.
December 12, 1990	Final printed labels and labeling.

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

IND
IND
IND
IND
IND
DMF
DMF
DMF

DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

4. Related Documents (INDs, NDAs, etc.):

None.

5. Facilities (Operation, Firm and Address):

New drug substance is manufactured by Sandoz Ltd., Basle, Switzerland.

Drug product is manufactured and packaged at Sandoz Pharmaceuticals, Inc., East Hanover, NJ.

Alternate facilities that may be used for packaging:

C. Remarks:
Isradipine is a calcium channel blocking agent which has been shown to have potent vasodilating properties and should be an effective antihypertensive agent.

November 26, 1986 amendment included trade and generic names assignment to the product.

October 24, 1986 amendment included responses to deficiencies.

July 20, 1987 amendment responded to the deficiencies noted in method validation

November 22, 1988 amendment included annotated labeling, draft c. package insert and draft container labels. Draft labels for 2.5 mg and 5 mg strengths in 30's 60's and 100's and SandoPak blisters and blister cartons were included. Package insert was satisfactory for DESCRIPTION and HOW SUPPLIED sections. Only 2.5 mg and 5 mg dosage strengths were listed. AT the present time only these strengths will be marketed.

November 17, 1989 amendment included draft copies of container carton labels for physician and pharmacy sample packages.

November 28, 1990 amendment includes the revised draft copy in response to FDA's "markup" copy received by the firm. DESCRIPTION and HOW SUPPLIED sections are satisfactory.

December 12, 1990 amendment included final printed labels and labeling for 2.5 mg and 5 mg strengths.

EI for all the facilities listed under Facilities was acceptable on 4/7/86. Additional EI requested on August 6, 1990. No report as of December 14, 1990.

Methods validations were performed by St. Louis and NY District laboratories. Methods are satisfactory for regulatory purposes.

EIAR - little or no effect on the environment is expected.

D. Conclusions and/or Recommendations:

Responses to deficiencies were satisfactory.

Next printing of the labeling, we recommend addition of the drug substance solubility information to the DESCRIPTION section of the package insert.

Danute G. Cunningham

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
19546R11

12-17-90

E. Review Notes:

December 12, 1990 amendment

Container labels (60's and 100's) for 2.5 mg and 5 mg strengths - satisfactory. Unit-dose containers (both strengths) - satisfactory. Blisters do not have lot # and expiration date on the blister, but the information are provided on the unit-dose containers.

Pakcage insert - DYN-21 December 1, 1990 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.

We recommend that on next printing, solubility information for the drug substance be added to the DESCRIPTION section of the insert.

DEC 27 1988

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW # 7

Date Completed: December 27, 1988

A. 1. NDA 19,546

Sponsor: Sandoz Pharmaceuticals Corp.
Route 10
East Hanover, NJ 07936

AF#: 19-463

2. Product Name (s): PN 200-110 Capsules

Amendment 11/26/86 - Dynacirc (isradipine) Capsules

Proprietary: Not yet established.

Amendment 11/26/86 - Dynacirc

Nonproprietary: Not yet established.

Amendment 11/26/86 - Isradipine

USAN: None.

Amendment 11/26/86 - Isradipine

Compendium: None.

Code Name and/or Number: PN 200-110 n
AW 200-110 n
200-110 n
200-110
200-110 base
200-110 b
PN 200-110

International Nonproprietary (INN,WHO): Isradipine

Patent Information: USP 4,446,972, expires August 21, 2001.

CAS Registry Number: 75695-93-1

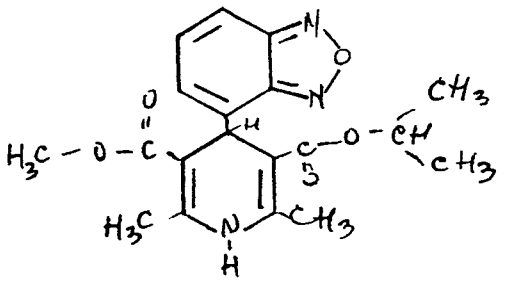
3. Dosage Form and Route of Administration:

2.5 mg., 5.0 mg., 7.5 mg. and 10 mg. capsules, for oral administration, Rx.

4. Pharmacological Category and/or Principal Indications:

Antihypertensive.

5. Structural Formula and Chemical Name:



Chemical names:
3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester.

Isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylate.

4-(2,1,3--Benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic acid, 3-methyl-5-(1-methylethyl)ester.

3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, 3-methyl-5-(1-methylethyl)ester.

Isopropyl methyl 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

4-(4-Benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylic acid, 3-methyl-5-(1-methylethyl)-ester.

Empirical Formula: $C_{19}H_{21}N_3O_5$

Molecular Weight: 371.39

MP: 166.0-170.0°C

B. 1. Initial Submission: December 27, 1985
Received CDB: December 27, 1985
Assigned: January 21, 1986

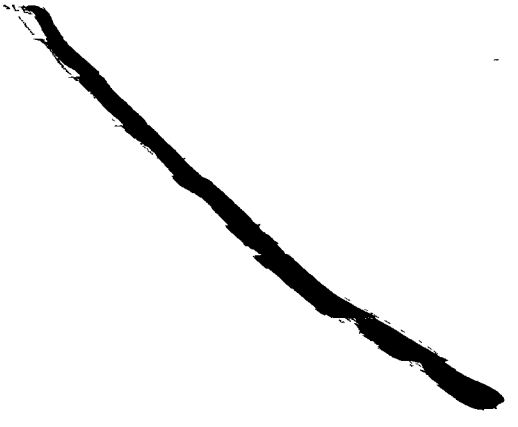
2. Amendments:

May 30, 1986 (summaries and labeling).
November 26, 1986 (chemistry, manufacturing and controls; non-clinical toxicology; human pharmacokinetics/bioavailability; clinical trials).
October 24, 1986 - response to deficiencies.
July 20, 1987 - responses to deficiencies in methods validation.
December 17, 1987 - change in branding for all strengths.

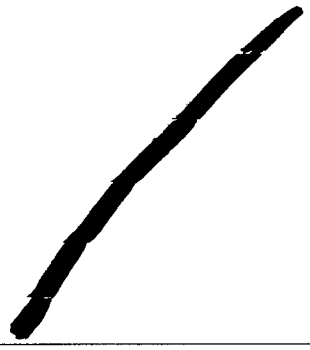
November 22, 1988 - Safety update and draft labeling.
December 21, 1988 - response to requested information.

3. Supporting INDs, NDAs, MFs and Letters of Authorizaton:

IND
IND
IND
IND
IND
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF



DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF



4. Related Documents (INDs, NDAs, etc.):

None.

C. Remarks:

PN 200-110 n is a calcium-channel blocking agent which has been shown to have potent vasodilating properties and should be an effective antihypertensive agent.

Additional stability data submitted with 11/26/86 amendment. Trade and generic names have been assigned. Labeling is satisfactory for bottle and blisters, and for DESCRIPTION and HOW SUPPLIED sections for the package insert.

October 24, 1986 amendment - contained answers to deficiencies listed in Chemist Review # 1.

July 20, 1987 amendment responded to deficiencies in methods validation.

December 17, 1987 amendment - change in branding for all strengths. Original branding consisted of the trade name of the drug, the dosage strength, and a design band featuring the Sandoz logo (a capital S inscribed inside a triangle). The new branding will feature an additional logo specifically develped for Dynacirc. Dynacirc and Dynacirc logo will be on one end, and the strength and Sandoz logo on the other end of capsules.

November 22, 1988 amendment - included annotated labeling, draft of package insert and draft container labels. Safety update was omitted from chemist's copy.

Draft labels for 2.5 mg and 5 mg strengths in 30's, 60's and 100's and Sandopak blisters and blister carton are included.

30's and 60's container labels do not have expiration date.

Blisters - do not have Lot # or expiration date.

Sandopak carton - does not have expiration date.

Package insert - Satisfactory for DESCRIPTION and HOW SUPPLIED sections. Only 2.5 mg and 5 mg dosage forms are listed.

12/15/88 - called Mr. Douglas W. Bitz (201-503-8604) - about the above labeling deficiencies. Also requested information if [redacted] be used as one of the packagers. On December 21, 1988 the requested information was received.

The expiration date will be printed "on line" directly below preprinted Quality Control No. on container/carton labels. The individual blisters will have both the lot no. and expiration date printed "on line" (December 21, 1988 correspondence).

At the present time only 2.5 mg and 5 mg dosage forms will be marketed.

D. Conclusions and/or Recommendations:

Deficiencies due to methods validation were answered in the amendment of July 20, 1987. Previous deficiencies were answered satisfactorily in the amendment of October 24, 1986.

EI is acceptable for all with the exception of [redacted] was notified. [redacted] will not be used (December 21, 1988 correspondence).

Methods validation satisfactory, done by St. Louis and NY-DO.

EIAR - little or no effect on environment expected.

Danute G. Cunningham

Danute G. Cunningham

cc:
Orig.
HFN-110
HFN-110/CSO
HFN-110/DGCunningham
Doc. # 0248c

FEB -7 1988

DIVISION OF CARDIO-RENAL NEW DRUG PRODUCTS
REVIEW AND EVALUATION OF MANUFACTURING CONTROLS DATA
CHEMIST'S REVIEW # 6

Date Completed: February 4, 1988

A. 1. NDA 19,546

Sponsor: Sandoz Pharmaceuticals Corp.
Route 10
East Hanover, NJ 07936

AF#: 19-463

2. Product Name (s): PN 200-110 Capsules

Amendment 11/26/86 - Dynacirc (isradipine) Capsules

Proprietary: Not yet established.

Amendment 11/26/86 - Dynacirc

Nonproprietary: Not yet established.

Amendment 11/26/86 - Isradipine

USAN: None.

Amendment 11/26/86 - Isradipine

Compendium: None.

Code Name and/or Number: PN 200-110 n
AW 200-110 n
200-110 n
200-110
200-110 base
200-110 b
PN 200-110

International Nonproprietary (INN,WHO): Isradipine

Patent Information: USP 4,446,972, expires August 21, 2001.

CAS Registry Number: 75695-93-1

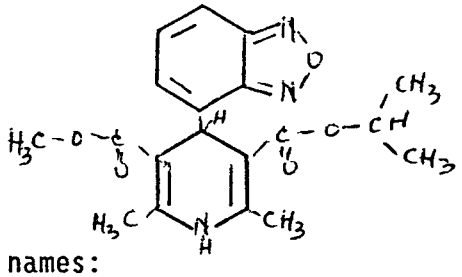
3. Dosage Form and Route of Administration:

2.5 mg., 5.0 mg., 7.5 mg. and 10 mg. capsules, for oral administration, Rx.

4. Pharmacological Category and/or Principal Indications:

Antihypertensive.

5. Structural Formula and Chemical Name:



Chemical names:
3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,5-dimethyl-, methyl 1-methylethyl ester.

Isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylate.

4-(2,1,3--Benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic acid, 3-methyl-5-(1-methylethyl)ester.

3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, 3-methyl-5-(1-methylethyl)ester.

Isopropyl methyl 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

4-(4-Benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylic acid, 3-methyl-5-(1-methylethyl)-ester.

Empirical Formula: $C_{19}H_{21}N_3O_5$

Molecular Weight: 371.39

MP: 166.0-170.0°C

B. 1. Initial Submission: December 27, 1985
Received CDB: December 27, 1985
Assigned: January 21, 1986

2. Amendments:

May 30, 1986 (summaries and labeling).
November 26, 1986 (chemistry, manufacturing and controls; non-clinical toxicology; human pharmacokinetics/bioavailability; clinical trials).
October 24, 1986 - response to deficiencies.
July 20, 1987 - responses to deficiencies in methods validation.
December 17, 1987 - change in branding for all strengths.

3. Supporting INDs, NDAs, MFs and Letters of Authorizaton:

IND
IND
IND
IND
IND
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

4. Related Documents (INDs, NDAs, etc.):

None.

C. Remarks:

PN 200-110 n is a calcium-channel blocking agent which has been shown to have potent vasodilating properties and should be an effective antihypertensive agent.

Additional stability data submitted with 11/26/86 amendment. Trade and generic names have been assigned. Labeling is satisfactory for bottle and blisters, and for DESCRIPTION and HOW SUPPLIED sections for the package insert.

October 24, 1986 amendment - contained answers to deficiencies listed in Chemist Review # 1.

July 20, 1987 amendment responded to deficiencies in methods validation.

December 17, 1987 amendment - change in branding for all strengths. Original branding consisted of the trade name of the drug, the dosage strength, and a design band featuring the Sandoz logo (a capital S inscribed inside a triangle). The new branding will feature an additional logo specifically develped for Dynacirc. Dynacirc and Dynacirc logo will be on one end, and the strength and Sandoz logo on the other end of capsules.

Only the appearance of the capsules are changed. The branding inks and capsule shell composition remains the same, as previously described in NDA.

In addition, included in the 12/17/87 amendment are the specification sheets from — for the capsules and specifications from — providing the composition of the branding inks.

Draft copy of HOW SUPPLIED section describing the physical appearance of the capsules is included.

D. Conclusions and/or Recommendations:

Deficiencies due to methods validation were answered in the amendment of July 20, 1987. Previous deficiencies were answered satisfactorily in the amendment of October 24, 1986.

EI is acceptable for all with the exception of ——
—— was notified.

Methods validation satisfactory, done by St. Louis and NY-DO.

EIAR - little or no effect on environment expected.

Danute G. Cunningham

Danute G. Cunningham

cc:
Orig.
HFN-110
HFN-110/CSO
HFN-110/DGCunningham
Doc. # 0055c

DIVISION OF CARDIO-RENAL NEW DRUG PRODUCTS
REVIEW AND EVALUATION OF MANUFACTURING CONTROLS DATA
CHEMIST'S REVIEW # 5

Date Completed: August 14, 1987

A. 1. NDA 19,546

Sponsor: Sandoz Pharmaceuticals Corp.
Route 10
East Hanover, NJ 07936

AF#: 19-463

2. Product Name (s): PN 200-110 Capsules

Amendment 11/26/86 - Dynacirc (isradipine) Capsules

Proprietary: Not yet established.

Amendment 11/26/86 - Dynacirc

Nonproprietary: Not yet established.

Amendment 11/26/86 - Isradipine

USAN: None.

Amendment 11/26/86 - Isradipine

Compendium: None.

Code Name and/or Number: PN 200-110 n
AW 200-110 n
200-110 n
200-110
200-110 base
200-110 b
PN 200-110

International Nonproprietary (INN,WHO): Isradipine

Patent Information: USP 4,446,972, expires August 21, 2001.

CAS Registry Number: 75695-93-1

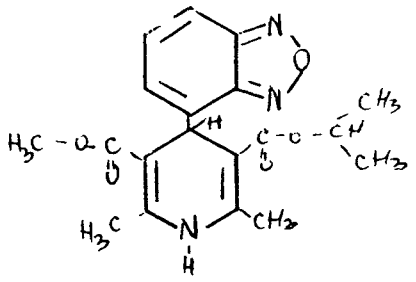
3. Dosage Form and Route of Administration:

2.5 mg., 5.0 mg., 7.5 mg. and 10 mg. capsules, for oral administration, Rx.

4. Pharmacological Category and/or Principal Indications:

Antihypertensive.

5. Structural Formula and Chemical Name:



Chemical names:
3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,5-dimethyl-, methyl 1-methylethyl ester.

Isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylate.

4-(2,1,3--Benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic acid, 3-methyl-5-(1-methylethyl)ester.

3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, 3-methyl-5-(1-methylethyl)ester.

Isopropyl methyl 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

4-(4-Benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylic acid, 3-methyl-5-(1-methylethyl)-ester.

Empirical Formula: $C_{19}H_{21}N_3O_5$

Molecular Weight: 371.39

MP: 166.0-170.00C

B. 1. Initial Submission: December 27, 1985
Received CDB: December 27, 1985
Assigned: January 21, 1986

2. Amendments:

May 30, 1986 (summaries and labeling).
November 26, 1986 (chemistry, manufacturing and controls; non-clinical toxicology; human pharmacokinetics/bioavailability; clinical trials).
October 24, 1986 - response to deficiencies.
July 20, 1987 - responses to deficiencies in methods validation.

3. Supporting INDs, NDAs, MFs and Letters of Authorizaton:

IND
IND
IND
IND
IND
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

[redacted]

)

4. Related Documents (INDs, NDAs, etc.):

None.

C. Remarks:

PN 200-110 n is a calcium-channel blocking agent which has been shown to have potent vasodilating properties and should be an effective antihypertensive agent.

Additional stability data submitted with 11/26/86 amendment. Trade and generic names have been assigned. Labeling is satisfactory for bottle and blisters, and for DESCRIPTION and HOW SUPPLIED sections for the package insert.

October 24, 1986 amendment - contained answers to deficiencies listed in Chemist Review # 1.

Responses to deficiencies in methods validation (July 20 1987 amendment):

1. Please revise the system suitability testing solution in the — procedure for the drug substance. As written, the quantity of — is present at —1% level (p. 03-00703) instead of —% as suggested on p. 03-00604. At — % level the impurity is not detectable at the specified settings. We suggest that equal quantities of isradipine and the impurity — be used for system suitability. The elution of peaks of similar heights not only facilitates the measurement of the resolution factor, but also gives a more accurate calculated result.

The system suitability testing solution has been revised to give a concentration of —% for the — relative to the isradipine. The specifications require a resolution between isradipine and — of at least —

This — concentration is closer to the amounts of — actually found. At this level, accurate calculation of the resolution factor can be achieved using commercially available computer-integration systems.

Revised tests and specifications are attached.

Acceptable.

2. Please specify in the assay of the drug substance by — that — used for the preparation of the mobile phase has to be preserved with — or make a note indicating the addition of a — as one of the constituents in the preparation of the mobile phase.

The — used to prepare the mobile phase has been clearly defined. The content of — has been specified in the specifications.

3. Please incorporate the — of the impurities into the purity testing procedure, and not just the comparison of sample to diluted standard solution preparations. The — of impurities in the purity testing of the drug substance by — would eliminate possible resolution problems due to variations in plate, RT, etc.

The purity testing procedure has been revised. Comparison solution 6 contains the known possible impurities and is — to demonstrate the resolution of the — Revised procedure is included. The impurities included in the solution 6 are — isradipine, — and are present at level.

Satisfactory.

4. In the dissolution testing for the capsules, please indicate if — are used to — the capsules. Slight variation in dissolution results was obtained depending on the use or omission of —

— are not used to — Dynacirc capsules during the dissolution test

Also included is a discussion of the use of lauryl dimethylamine oxide as surfactant in the dissolution testing procedure.

Isradipine is poorly soluble in the media commonly used for dissolution. Its solubility in water, 0.1N HCl, pH 4.0 acetate buffer and pH 6.8 phosphate buffer is less than 5 mg/L. This solubility is insufficient to maintain sink conditions for all capsule strengths (up to 10 mg) described in this NDA. Therefore a dissolution medium containing a surfactant was selected in late 1984.

There was no established preference for any particular surfactant. The objective was to select a surfactant which could be used, in as small an amount as possible, to increase the solubility of isradipine to nlt — mg/L. This was achieved with 0.1% lauryl dimethylamine oxide (LDAO). With the same level sodium laury sulfate the solubility of isradipine is only — mg/L.

The proposed dissolution test conditions are as follows:

Apparatus:	USP Apparatus 2, paddle
Rotation speed:	50 rpm
Dissolution medium:	500 mL or 1000 mL of 0.1% (w/v) LDAO in water (volume dependent on the capsule strength).
Requirement:	Q=— % in 60 min.

These conditions have been used to obtain all results for the stability database.

D. Conclusions and/or Recommendations:

Deficiencies due to methods validation were answered in the amendment of July 20, 1987. Previous deficiencies were answered satisfactorily in the amendment of October 24, 1986.

EI is acceptable for all with the exception of —— was notified.

Methods validation satisfactory, done by St. Louis and NY-DO.

EIAR - little or no effect on environment expected.

Danute G. Cunningham

Danute G. Cunningham

cc:
Orig.
HFN-110
HFN-110/CSO
HFN-110/DGCunningham
Doc. # 0441D

MAR 9

DIVISION OF CARDIO-RENAL NEW DRUG PRODUCTS
CHEMIST'S REVIEW # 4

Date Completed: March 5, 1987

A. 1. NDA 19,546

Sponsor: Sandoz Pharmaceuticals Corp.
Route 10
East Hanover, NJ 07936

AF#: 19-463

---

2. Product Name (s): PN 200-110 Capsules

Amendment 11/25/86 - Dynacirc (isradipine) Capsules

Proprietary: Not yet established.

Amendment 11/26/86 - Dynacirc

Nonproprietary: Not yet established.

Amendment 11/26/86 - Isradipine

USAN: None.

Amendment 11/26/86 - Isradipine

Compendium: None.

Code Name and/or Number: PN 200-110 n
AW 200-110 n
200-110 n
200-110
200-110 base
200-110 b
PN 200-110

International Nonproprietary (INN,WHO): Isradipine

Patent Information: USP 4,446,972, expires August 21, 2001.

CAS Registry Number: 75695-93-1

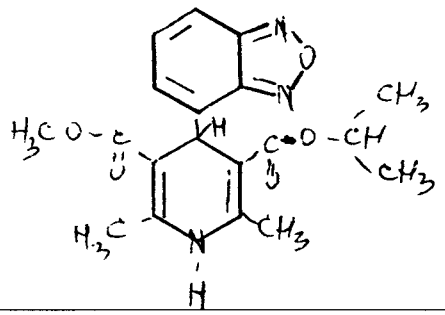
3. Dosage Form and Route of Administration:

2.5 mg., 5.0 mg., 7.5 mg. and 10 mg. capsules, for oral administration, Rx.

4. Pharmacological Category and/or Principal Indications:

Antihypertensive.

5. Structural Formula and Chemical Name:



Chemical names:
3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,5-dimethyl-, methyl 1-methylethyl ester.

Isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylate.

4-(2,1,3--Benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic acid, 3-methyl-5-(1-methylethyl)ester.

3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, 3-methyl-5-(1-methylethyl)ester.

Isopropyl methyl 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

4-(4-Benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylic acid, 3-methyl-5-(1-methylethyl)-ester.

Empirical Formula: $C_{19}H_{21}N_3O_5$

Molecular Weight: 371.39

MP: 166.0-170.0°C

B. 1. Initial Submission: December 27, 1985
Received CDB: December 27, 1985
Assigned: January 21, 1986

2. Amendments:

May 30, 1986 (summaries and labeling).
November 26, 1986 (chemistry, manufacturing and controls; non-clinical toxicology; human pharmacokinetics/bioavailability; clinical trials).
October 24, 1986 - response to deficiencies.

3. Supporting INDs, NDAs, MFs and Letters of Authorizaton:

IND
IND
IND
IND
IND
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

4. Related Documents (INDs, NDAs, etc.):

None.

C. Remarks:

PN 200-110 n is a calcium-channel blocking agent which has been shown to have potent vasodilating properties and should be effective antihypertensive agent.

Additional stability data submitted with 11/26/86 amendment. Trade and generic name has been assigned. Labeling is satisfactory for bottle and blisters, and for DESCRIPTION and HOW SUPPLIED sections for the package insert.

EI is acceptable for all with the exception of [redacted] was notified.

October 24, 1986 amendment - contains answers to deficiencies.

Methods validation satisfactory, done by St. Louis and NY-DO.

. Conclusions and/or Recommendations:

Deficiencies due to methods validation are listed in the Draft Letter to Applicant. Previous deficiencies were answered satisfactorily.

Danute G. Cunningham

cc:
Orig.
HFN-110
HFN-110/CSO
HFN-110/DGCunningham
Doc. # 0209D

3/9/87

DIVISION OF CARDIO-RENAL NEW DRUG PRODUCTS
CHEMIST'S REVIEW # 1

Date Completed: March 3, 1986

A. 1. NDA 19,546

Sponsor: Sandoz Pharmaceuticals Corp.
Route 10
East Hanover, NJ 07936

AF#: 19-463

2. Product Name (s): PN 200-110 Capsules

Proprietary: Not yet established.

~~Nonproprietary: Not yet established.~~

USAN: None.

Compendium: None.

Code Name and/or Number: PN 200-110 n
AW 200-110 n
200-110 n
200-110
200-110 base
200-110 b
PN 200-110

International Nonproprietary (INN,WHO): Isrodipine

Patent Information: USP 4,446,972, expires August 21, 2001.

CAS Registry Number: 75695-93-1

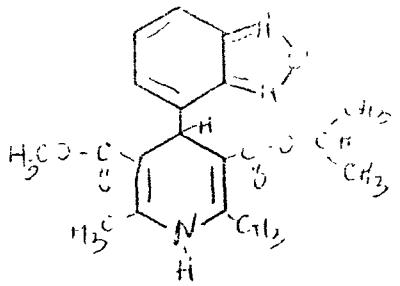
3. Dosage Form and Route of Administration:

2.5 mg., 5.0 mg., 7.5 mg. and 10 mg. capsules, for oral administration, Rx.

4. Pharmacological Category and/or Principal Indications:

Antihypertensive.

5. Structural Formula and Chemical Name:



Chemical names:
3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,5-dimethyl-, methyl 1-methylethyl ester.

~~Isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-~~ 2,6-dimethyl-3-pyridinecarboxylate.

4-(2,1,3--Benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic acid, 3-methyl-5-(1-methylethyl)ester.

3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, 3-methyl-5-(1-methylethyl)ester.

Isopropyl methyl 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

4-(4-Benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylic acid, 3-methyl-5-(1-methylethyl)-ester.

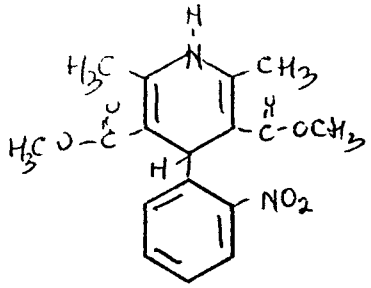
Empirical Formula: $C_{19}H_{21}N_3O_5$

Molecular Weight: 371.39

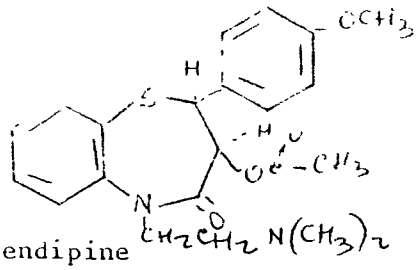
MP: 166.0-170.0°C

Related Drugs

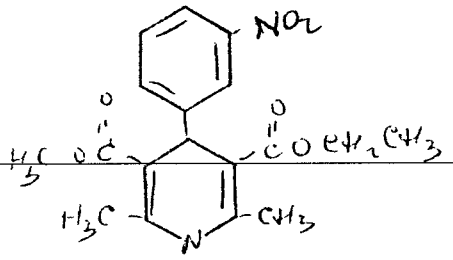
Nifedipine



Dilthiazem



Nitrendipine



B. 1. Initial Submission: December 27, 1985
Received CDB: December 27, 1985
Assigned: January 21, 1986

2. Amendments:

None.

3. Supporting INDs, NDAs, MFs and Letters of Authorizaton:

IND
IND
IND
IND
IND
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

DMF
DMF
DMF
DMF
DMF

4. Related Documents (INDs, NDAs, etc.):

None.

C. Remarks:

PN 200-110 n is a calcium-channel blocking agent which has been shown to have potent vasodilating properties and should be effective antihypertensive agent.

This is a preassigned NDA.

D. Conclusions and/or Recommendations:

Deficiencies are listed in the Draft Letter to Applicant.

Danute G. Cunningham
Danute G. Cunningham

cc:
Orig.
HFN-102/CKumkumian
HFN-110
HFN-110/CSO
HFN-110/DGCunningham
Doc. # 9113c

3/7/84