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CHEM
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW

NDA 12-486
Data Completed: December 14, 1990

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

    NDC: 12-463

    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


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 Structure Image]
Chemical Name (s):

3,5-Pyridinedicarboxylic acid, 4-(4-phenylfuran-2-yl)-2,5-dimethyl-3-methyl-1-methyl-1-ethylyl ether

Isopropyl 4-(2,2,2-trifluorophenyl)-3,5-dimethyl-3-methyl-1-ethylyl ether

4-(2,2-Dimethyl-3-methyl-3,5-dimethyl-3-ethylcarboxylic acid, 5-ethyl-1-(1-ethylyl)-ester

3,5-Pyridinedicarboxylic acid, 4-(4-phenylfuran-2-yl)-2,5-dimethyl-3-methyl-1-ethylyl ether

Molecular Formula: C_{22}H_{28}N_{10}O_{2}

Molecular Weight: 401.39

MP: 156.0-170.5°C

B. Initial Submission:

Data Submitted: December 27, 1985
Data Received: December 27, 1985
Date to Chemist: January 21, 1986

2. Amendments:

May 30, 1986
November 16, 1986
October 24, 1986
July 20, 1987
December 17, 1987
November 22, 1988
December 21, 1988
November 17, 1989
May 11, 1990
November 28, 1990
December 12, 1990

Summaries and labeling.
Chemistry, manufacturing and controls information.
Response to deficiencies.
Response to deficiencies in methods validation.
Change in branding for all strengths.
Safety update and draft labeling.
Response to information request.
Draft labeling for physician and pharmacy sample packages.
Revision in DESCRIPTION section of package insert.
Revised draft labeling.
Final printed labels and labeling.

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

- IND
- IND
- IND
- IND
- IND
- 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, 1986 amendment included annotated labeling, draft e.
package insert and draft container labels. Draft labels for 2.5 mg and
5 mg strengths in 10's, 60's, and 100's and SandPak blisters and blister
carriers 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 23, 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.

cc:

Orig.

HFD-110

HFD-110/CSO

HTU-111/DGCunningham

19546R1
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.

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

We recommend that on next printing, solubility information for the drug be added to the DESCRIPTION section of the insert.
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 11/26/85 - 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


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 Structure]

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

Isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-3-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-(1-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_{3}O_{5}
Molecular Weight: 371.39
MP: 155.0-170.0°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 Authorization:
   IND
   IND
   IND
   IND
   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 developed 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 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 _______ was notified. _______ 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.

CC: 

Danute G. Cunningham

Danute G. Cunningham
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
AM 200-110 n
200-110 n
200-110
200-110 base
200-110 b
PN 200-110
International Nonproprietary (INN, WHO): Isradipine


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:

\[
\text{Chemical names: 3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazany)-1,4-dihydro-2,5-dimethyl-, methyl 1-methylethyl ester.}
\]

Isopropyl 4-(2,1,3-benzoxadiazol-4-y1)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylate.

4-(2,1,3-Benzoxadiazol-4-y1)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic acid, 3-methyl-5-(1-methylethyl)ester.

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

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

4-(4-Benzofurazany)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylic acid, 3-methyl-5-(1-methylethyl)-ester.
Empirical Formula: $C_{19}H_{21}N_{3}O_{5}$

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).
   December 17, 1987 – change in branding for all strengths.

3. **Supporting INDs, NDAs, MFs and Letters of Authorization:**

   IND
   IND
   IND
   IND
   IND
   DMF
   DMF
   DMF
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   DMF
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   DMF
   DMF
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   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 developed 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 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.

cc:
Orig.

Danute G. Cunningham

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 11/25/86 - Isradipine

USAN: None.

Amendment 11/25/86 - 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


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 Structure](image)

   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-Benzoaxadiazol-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-dicar-
   boxylic acid, 3-methyl-5-(1-methylethyl)-ester.

   Empirical Formula: C_{19}H_{21}N_{3}O_{5}

   Molecular Weight: 371.39

   MP: 166.0-170.00°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.
3. Supporting INDs, NDAs, NIs and Letters of Authorization:

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

None.

C. Remarks:

PN 200-110 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 1937 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 1% as suggested on p. 03-00694. At 1% 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 1% for the relative to the isradipine. The specifications require a resolution between isradipine and 1% of at least 5.

This 5% concentration is closer to the amounts of 1% 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 1 as one of the constituents in the preparation of the mobile phase.

The 1 used to prepare the mobile phase has been clearly defined. The content of 1 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 1 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 5.3 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 lauryl 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.

cc: 
Orig.
**HFN-110**
HFN-110/CSO
HFN-110/DGCunningham
Doc. # 0441D
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 07935

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 11/26/85 - 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


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 Structure](image)

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_{3}O_{5}

Molecular Weight: 371.39

MP: 166.0-170.00°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 Authorization:

IND
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DMF
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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 ______ 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
A. 1. NDA 19,540

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

AP#: 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): Isodipine


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 Structure](image)

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

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

4-(2,1,3-Benzoaxidiazol-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:** C₁₉H₂₁N₃₅

**Molecular Weight:** 371.39

**MP:** 166.0-170.0°C

**Related Drugs**

**Nifedipine**

![Chemical Structure](image)
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 Authorization:**  
IND  
IND  
IND  
IND  
IND  
IND  
DMF  
DMF  
DMF  
DMF  
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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.

\[\text{Signature}\]
Danute G. Cunningham

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