CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074817

Trade Name : INVAGESIC AND INVAGESIC FORTE

Generic Name:Aspirin, Caffine and Orphenadrine Citrate

Sponsor : Invamed, Inc.

Approval Date: November 11, 1996

ANDA 74-817

NOV 27 1996

Invamed Inc.
Attention: Mahendra R. Patel, Ph.D.
2400 Route 130 North
Dayton, NJ 08810

Dear Sir:

This is in reference to your abbreviated new drug application dated December 26, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Invagesic™ and Invagesic™ Forte (Aspirin, Caffeine, and Orphenadrine Citrate) Tablets, 385 mg/30 mg/25 mg and 770 mg/60 mg/50 mg.

Reference is also made to your amendments dated June 20, September 25, and October 23, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Invagesic™ and Invagesic™ Forte (Aspirin, Caffeine and Orphenadrine Citrate) Tablets, 385 mg/30 mg/25 mg and 770 mg/60 mg/50 mg, respectively are bioequivalent, and, therefore, therapeutically equivalent, to those of the listed drugs (Norgesic® and Norgesic® Forte Tablets, 385 mg/30 mg/25 mg and 770 mg/60 mg/50 mg, respectively, of 3M Pharmaceuticals, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method as proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

D. L. Sporn 11/27/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Addendum to Chemist's Review # 2 For pending issues:

ANDA 74-817

1. Chemistry Issues were previously closed - See Review # 2 for this ANDA.

2. EER submitted on 12-29-95 for all facilities listed in CR # 2 of ANDA became acceptable on 10-22-96 and 11-18-96. Note that the unacceptable status for has been changed to acceptable by Mark Lynch of OC.

3. Methods Validation: Satisfactory per MV package dated 11-12-96 from Philadelphia laboratory.

4. FPL - acceptable per review completed by C. Holquist on 7-5-96.

Since completion of CR # 2, no change in USP 23 requirements for the active ingredients used in the drug product is noted by this reviewer. No change in DMF status is noted since completion of CR # 2.

Conclusion: ANDA is approvable.

c.c: ANDA 74-817
Division File
FIELD COPY

Endorsements:

HFD-625/M. Shaikh/11/18/96 S. Shaikh for Shaikh 10/26/96
HFD-625/M. Smela/11/19/96 M Smela 11/26/96
F/t by: gp/11/22/96
x:\new\firmsam\invamed\ltrs&rev\74817rev2.ad1

Chem Closed

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-817

3. NAME AND ADDRESS OF APPLICANT
Invamed Inc.
2400 Route 130
Dayton, NJ 08810

4. BASIS OF SUBMISSION
Acceptable per CR # 1 completed by this reviewer.

The listed drug product is Norgesic and Norgesic Forte Tablets by 3M Pharmaceutical, CA approved in NDA # 13-416 003 and 13-416 004, respectively.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Invagesic Tablets and Invagesic Forte Tablets

7. NONPROPRIETARY NAME
Aspirin, Caffeine and Orphenadrine Citrate Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-26-95
Amendment: 2-8-96
* Minor Amendment: 6-20-96 (Response to NA letter dated 5-31-96)

FDA:
Refuse to File: 2-2-96
Accepted for filing: 2-9-96 (Acknowledgement letter issued on 3-11-96).
NA letter: 5-31-96

10. PHARMACOLOGICAL CATEGORY
Relief from moderate pain and discomfort due to acute muscular skeletal disorder

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets

14. POTENCY
Invagesic Tablets: 385 mg/30 mg/25 mg
Invagesic Forte Tablets: 770 mg/60 mg/50 mg

15. CHEMICAL NAME AND STRUCTURE
See CR # 1.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Invamed has provided adequate information regarding components and composition, processing and manufacturing, controls, and stability of these drug products. Supporting DMFs are adequate. Bio status - acceptable per May 31, 1996 letter to the firm. Invamed provided adequate stability data to support their expiration dating period of 24 months.

EER status is pending. Samples for MV are being requested by the Philadelphia District.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable EER status and satisfactory MV.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 7-9-96

cc: ANDA 74-817
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/7-9-96 Mujahid Shaikh 7/11/96
HFD-625/M.Smela/7-10-96
x:\new\firmsam\Invamed\ltrs&rev\74817REV.2
F/T by: bc/7-10-96

M.D. Smela 7/11/96

ASPIRIN, CAFFEINE AND ORPHENADRINE CITRATE TABLETS,
385 mg/30 mg/25 mg and 770 mg/60 mg/50 mg
ANDA # 74-817
MINOR AMENDMENT
(RESPONSE TO FDA LETTER DATED 05/31/96)

NDC 52189-266-29

invamed inc.

Invagesic™ Forte Tablets

(Orphenadrine citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

EACH TABLET CONTAINS:

Orphenadrine citrate	50 mg
Aspirin	770 mg
Caffeine	60 mg

USUAL DOSAGE: Adults: One-half to one tablet three to four times daily. See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store below 30°C (86°F).
Protect from moisture.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

3 52189-266-29 7

Lot No.:
Exp. Date:
MF # 888

NDC 52189-266-29

invamed inc.

Invagesic™ Forte Tablets

(Orphenadrine citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

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INVAMED INC., Dayton, NJ 08810 USA

3 52189-266-29 7

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Store below 30°C (86°F).
Protect from moisture.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

3 52189-266-29 7

Lot No.:
Exp. Date:
MF # 888

NDC 52189-265-30

invamed inc.

Invagesic™ Tablets

(Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

EACH TABLET CONTAINS:

Orphenadrine citrate	25 mg
Aspirin	385 mg
Caffeine	30 mg

USUAL DOSAGE: Adults: One to two tablets three to four times daily. See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store below 30°C (86°F). Protect from moisture.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

3 52189-265-30 6

Lot No.:
Exp. Date:
MF # 886

NDC 52189-265-30

invamed inc.

Invagesic™ Tablets

(Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

EACH TABLET CONTAINS:
Orphenadrine citrate 25 mg
Aspirin 385 mg
Caffeine 30 mg

USUAL DOSAGE: Adults: One to two tablets three to four times daily. See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store below 30°C (86°F). Protect from moisture.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

3 52189-265-30 6

Lot No.:
Exp. Date:
MF # 886

NDC 52189-265-30

invamed inc.

Invagesic™ Tablets

(Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

EACH TABLET CONTAINS:
Orphenadrine citrate 25 mg
Aspirin 385 mg
Caffeine 30 mg

USUAL DOSAGE: Adults: One to two tablets three to four times daily. See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store below 30°C (86°F). Protect from moisture.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

3 52189-265-30 6

Lot No.:
Exp. Date:
MF # 886

NDC 52189-265-30

invamed inc.

Invagesic™ Tablets

(Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

EACH TABLET CONTAINS:
Orphenadrine citrate 25 mg
Aspirin 385 mg
Caffeine 30 mg

USUAL DOSAGE: Adults: One to two tablets three to four times daily. See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store below 30°C (86°F). Protect from moisture.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

3 52189-265-30 6

Lot No.:
Exp. Date:
MF # 886

ASPIRIN, CAFFEINE AND ORPHENADRINE CITRATE TABLETS,
385 mg/30 mg/25 mg and 770 mg/60 mg/50 mg
ANDA # 74-817
MINOR AMENDMENT
(RESPONSE TO FDA LETTER DATED 05/31/96)

NDC 52189-265-29

invamed inc.

Invagesic™ Tablets

(Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

EACH TABLET CONTAINS:
Orphenadrine citrate ..... 25 mg
Aspirin ..... 385 mg
Caffeine ..... 30 mg

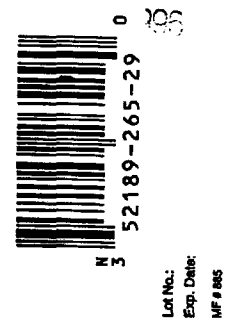
USUAL DOSAGE: Adults: One to two tablets three to four times daily. See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store below 30°C (86°F).
Protect from moisture.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



NDC 52189-265-29

invamed inc.

Invagesic™ Tablets

(Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

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EACH TABLET CONTAINS:
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Aspirin ..... 385 mg
Caffeine ..... 30 mg

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Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

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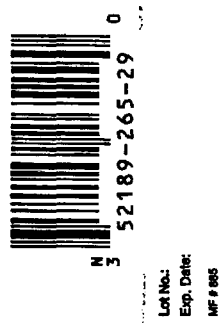
Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



NDC 52189-265-29

invamed inc.

Invagesic™ Tablets

(Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

EACH TABLET CONTAINS:
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Aspirin ..... 385 mg
Caffeine ..... 30 mg

USUAL DOSAGE: Adults: One to two tablets three to four times daily. See accompanying prescribing information.

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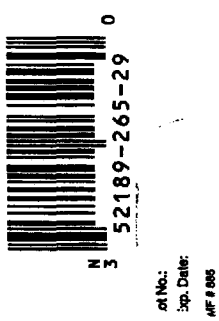
Manufactured By:



NDC 52189-265-29

invamed inc.

Invagesic™ Tablets

(Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

EACH TABLET CONTAINS:
Orphenadrine citrate ..... 25 mg
Aspirin ..... 385 mg
Caffeine ..... 30 mg

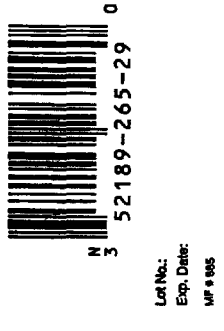
USUAL DOSAGE: Adults: One to two tablets three to four times daily. See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store below 30°C (86°F).
Protect from moisture.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



NDC 52189-265-24

invamed inc.

Invagesic™ Tablets

(Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

EACH TABLET CONTAINS:

Orphenadrine citrate	25 mg
Aspirin	385 mg
Caffeine	30 mg

USUAL DOSAGE: Adults: One to two tablets three to four times daily. See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store below 30°C (86°F).
Protect from moisture.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-265-24 5

Lot No.:
Exp. Date:
MF # 864

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NDC 52189-266-24

invamed inc.

Invagesic™ Forte Tablets

(Orphenadrine citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg Tablets)

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

EACH TABLET CONTAINS:

Orphenadrine citrate	50 mg
Aspirin	770 mg
Caffeine	60 mg

USUAL DOSAGE: Adults: One-half to one tablet three to four times daily. See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store below 30°C (86°F).
Protect from moisture.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-266-24 2

Lot No.:
Exp. Date:
MF # 867

Invagesic™
(Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg)

AND

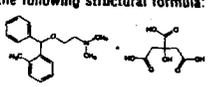
Invagesic Forte™
(Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg)

TABLETS

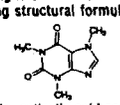
DESCRIPTION:

Each Invagesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) tablet intended for oral administration contains orphenadrine citrate 25 mg, aspirin 385 mg, and caffeine 30 mg. Each Invagesic Forte (Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg) tablet intended for oral administration contains orphenadrine citrate 50 mg, aspirin 770 mg, and caffeine 60 mg. Invagesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/ 30 mg) and Invagesic Forte (Orphenadrine Citrate, Aspirin and Caffeine 50 mg/ 770 mg/60 mg) Tablets also contain the following inactive ingredients: corn starch, croscarmellose sodium, D&C Yellow No. 10 aluminum lake, FD&C Blue No. 1 aluminum lake, lactose monohydrate, magnesium stearate, povidone and silicon dioxide.

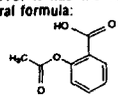
Orphenadrine citrate is the citrate salt of orphenadrine. It occurs as a white, crystalline powder having a bitter taste. It is practically odorless; sparingly soluble in water, slightly soluble in alcohol. The chemical name of orphenadrine citrate is (±)-*N,N*-Dimethyl-2-[(*o*-methyl-α-phenylbenzyl)oxy]ethylamine citrate (1:1) having molecular formula $C_{18}H_{23}NO \cdot C_6H_8O_7$ and molecular weight of 461.51. It has the following structural formula:



Caffeine is a central nervous system stimulant which occurs as white powder as white-glistering needles. It is practically odorless and has a bitter taste. It is sparingly soluble in water, alcohol, and freely soluble in chloroform. The chemical name for caffeine is 1,3,7-trimethylxanthine, having a molecular formula $C_8H_{10}N_4O_2$ and molecular weight of 194.19. It has the following structural formula:



Aspirin, salicylic acid acetate, is a non-opiate analgesic, anti-inflammatory and antipyretic agent. It occurs as a white, crystalline tabular or needle and is odorless. The molecular formula for aspirin is $C_9H_8O_4$ having a molecular weight of 180.16. It has the following structural formula:



CLINICAL PHARMACOLOGY:

Orphenadrine citrate is a centrally acting (brain stem) compound which in animals selectively blocks facilitatory functions of the reticular formation. Orphenadrine does not produce myoneural block, nor does it affect crossed extensor reflexes. Orphenadrine prevents nicotine-induced convulsions but

CLINICAL PHARMACOLOGY:

Orphenadrine citrate is a centrally acting (brain stem) compound which in animals selectively blocks facilitatory functions of the reticular formation. Orphenadrine does not produce myoneural block, nor does it affect crossed extensor reflexes. Orphenadrine prevents nicotine-induced convulsions but not those produced by strychnine.

Chronic administration of Invagesic to dogs and rats has revealed no drug-related toxicity. No blood or urine changes were observed, nor were there any macroscopic or microscopic pathological changes detected. Extensive experience with combinations containing aspirin and caffeine has established them as safe agents. The addition of orphenadrine citrate does not alter the toxicity of aspirin and caffeine.

The mode of therapeutic action of orphenadrine has not been clearly identified, but may be related to its analgesic properties. Orphenadrine citrate also possesses anticholinergic actions.

INDICATIONS AND USAGE:

Invagesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) and Invagesic Forte (Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg) Tablets are indicated in:

1. Symptomatic relief of mild to moderate pain of acute musculoskeletal disorders.
2. The orphenadrine component is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute painful musculoskeletal conditions.

The mode of action of orphenadrine has not been clearly identified, but may be related to its analgesic properties. Invagesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) and Invagesic Forte (Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg) Tablets do not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS:

Because of the mild anticholinergic effect of orphenadrine, Invagesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) or Invagesic Forte (Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg) Tablets should not be used in patients with glaucoma, pyloric or duodenal obstruction, achalasia, prostatic hypertrophy or obstructions at the bladder neck. Invagesic

(Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) or Invagesic Forte (Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg) Tablets are also contraindicated in patients with myasthenia gravis and in patients known to be sensitive to aspirin or caffeine.

The drug is contraindicated in patients who have demonstrated a previous hypersensitivity to the drug.

WARNINGS:

Reye's Syndrome may develop in individuals who have chicken pox, influenza, or flu symptoms. Some studies suggest a possible association between the development of Reye's Syndrome and the use of medicines containing salicylate or aspirin. Invagesic and Invagesic Forte contain aspirin and therefore are not recommended for use in patients with chicken pox, influenza, or flu symptoms.

Invagesic and Invagesic Forte may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; ambulatory patients should therefore be cautioned accordingly.

Aspirin should be used with extreme caution in the presence of peptic ulcers and coagulation abnormalities.

USAGE IN PREGNANCY: Since safety of the use of this preparation in pregnancy, during lactation, or in the childbearing age has not been established, use of the drug in such patients requires that the potential benefits of the drug be weighed against the hazard to the mother and child.

USAGE IN CHILDREN: The safe and effective use of this drug in children has not been established. Usage of this drug in children under 12 years of age is not recommended.

PRECAUTIONS:

Confusion, anxiety and tremors have been reported in a few patients receiving propoxyphene and orphenadrine concomitantly. As these symptoms may be simply due to an additive effect, reduction of dosage and/or discontinuation of one or both agents is recommended in such cases.

Safety of continuous long term therapy with Invagesic and Invagesic Forte has not been established; therefore, if Invagesic or Invagesic Forte is prescribed for prolonged use, periodic monitoring of blood, urine and liver function values is recommended.

ADVERSE REACTIONS:

Side effects of Invagesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) or Invagesic Forte (Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg) Tablets are those seen with aspirin and caffeine or those usually associated with mild anticholinergic agents. These may include tachycardia, palpitation, urinary hesitancy or retention, dry mouth, blurred vision, dilatation of the pupil, increased intraocular tension, weakness, nausea, vomiting, headache, dizziness, constipation, drowsiness, and rarely, urticaria and other dermatoses. Infrequently, an elderly patient may experience some degree of confusion. Mild central excitation and occasional hallucinations may be observed. These mild side effects can usually be eliminated by reduction in dosage. One case of aplastic anemia associated with the use of Invagesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) Tablets has been reported. No causal relationship has been established. Rare G.I. hemorrhage due to aspirin content may be associated with the administration of Invagesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) or Invagesic Forte (Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg) Tablets. Some patients may experience transient episodes of lightheadedness, dizziness or syncope.

DOSAGE AND ADMINISTRATION:

Invagesic: Adults 1 to 2 tablets 3 to 4 times daily.

Invagesic Forte: Adults ½ to 1 tablet 3 to 4 times daily.

HOW SUPPLIED:

Invagesic tablets are green/white, round, bi-layered, compressed, unscored, engraved INV over 265 on one side and are supplied as follows:

NDC 52189-265-24 in bottles of 100 tablets

NDC 52189-265-29 in bottles of 500 tablets

NDC 52189-265-30 in bottles of

tion of dosage and/or discontinuation of one or both agents is recommended in such cases.

Safety of continuous long term therapy with Invagesic and Invagesic Forte has not been established; therefore, if Invagesic or Invagesic Forte is prescribed for prolonged use, periodic monitoring of blood, urine and liver function values is recommended.

ADVERSE REACTIONS:

Side effects of Invagesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) or Invagesic Forte (Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg) Tablets are those seen with aspirin and caffeine or those usually associated with mild anticholinergic agents. These may include tachycardia, palpitation, urinary hesitancy or retention, dry mouth, blurred vision, dilatation of the pupil, increased intraocular tension, weakness, nausea, vomiting, headache, dizziness, constipation, drowsiness, and rarely, urticaria and other dermatoses. Infrequently, an elderly patient may experience some degree of confusion. Mild central excitation and occasional hallucinations may be observed. These mild side effects can usually be eliminated by reduction in dosage. One case of aplastic anemia associated with the use of Invagesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) Tablets has been reported. No causal relationship has been established. Rare G.I. hemorrhage due to aspirin content may be associated with the administration of Invagesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) or Invagesic Forte (Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg) Tablets. Some patients may experience transient episodes of lightheadedness, dizziness or syncope.

DOSAGE AND ADMINISTRATION:

Invagesic: Adults 1 to 2 tablets 3 to 4 times daily.

Invagesic Forte: Adults ½ to 1 tablet 3 to 4 times daily.

HOW SUPPLIED:

Invagesic tablets are green/white, round, bi-layered, compressed, unscored, engraved INV over 265 on one side and are supplied as follows:

NDC 52189-265-24 in bottles of 100 tablets

NDC 52189-265-29 in bottles of 500 tablets

NDC 52189-265-30 in bottles of 1000 tablets.

Invagesic Forte tablets are green/white, capsule-shaped, bi-layered, compressed, engraved INV to the left and 266 to the right of the bisect on one side and are supplied as follows:

NDC 52189-266-24 in bottles of 100 tablets

NDC 52189-266-29 in bottles of 500 tablets.

Store below 30°C (86°F). Protect from moisture.

Dispense in a tight, light-resistant container as defined in the USP.

CAUTION:

Federal law prohibits dispensing without prescription.

Manufactured by:
INVAMED, INC.
Dayton, NJ 08810 USA

Date of Revision: June 1996
[L-992; MF#889A]

ANDA 74-817

MAY 3 1 1996

Invamed, Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130 North
Dayton NJ 08810

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Aspirin, Caffeine, and Orphenadrine Citrate Tablets 385 mg, 30 mg, 25 mg and 770 mg, 60 mg, 50 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less thar of the labeled amount of the drug in the dosage form is dissolved in 45 minutes for Aspirin and Caffeine.

   Not less thar of the labeled amount of the drug in the dosage form is dissolved in 60 minutes for Orphenadrine Citrate.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAY 24 1996

Orphenadrine Citrate/Aspirin/Caffeine
50 mg/770 mg/60 mg Tablet
25 mg/385 mg/30 mg Tablet
ANDA #74-817
Reviewer: Moheb H. Makary
WP 74817SDW.D95

Invamed Inc.
Dayton, N.J.
Submission Date:
December 26, 1985

Review of a Bioequivalence Study, Dissolution Data and Waiver Request

I. Objective:

The objective of this study was to compare the plasma levels of orphenadrine, aspirin (salicylic acid) and caffeine, after administration of single dose of 50 mg/770 mg/60 mg of the test formulation (Invamed's Orphenadrine Citrate, Aspirin, and Caffeine Tablet, 50 mg/770 mg/60 mg) with that of 3M reference product (Norgesic^{R} Forte Tablet, 50 mg/770 mg/60 mg) under fasting conditions. The firm requested a waiver of the in vivo bioequivalence testing requirements for its 25 mg/385 mg/30 mg strength. Dissolution profiles comparing Invamed's Orphenadrine Citrate, Aspirin and Caffeine , 50 mg/770 mg/60 mg and 25 mg/385 mg/30 mg tablets and Norgesic® 50 mg/770 mg/60 mg and 25 mg/385 mg/30 mg tablets were submitted. Comparative compositions were also submitted.

II. Introduction:

Orphenadrine is an analogue of the antihistamine, diphenhydramine. It is a centrally acting (brain stem) compound indicated, in combination with aspirin and caffeine, for the symptomatic relief of mild to moderate pain of acute musculoskeletal disorders.

Both orphenadrine and the salicylate (the active metabolites of aspirin) reach peak plasma levels several hours after oral dosing. The elimination half-life of orphenadrine is about 14-16 hours, that of aspirin is 0.25 hour, the salicylate 3-12 hours and caffeine about 5 hours.

The combination product is commercially available as Norgesic^{R}, manufactured by 3M pharmaceuticals.

III. Single Dose Bioequivalence Study #B-01145 Under Fasting conditions:

Clinical site:

Analytical site:

Sponsor: Invamed Inc.
Dayton, NJ.

Study design: A single-dose, randomized, two-treatment, two-period, two-sequence crossover design.

Subjects: Twenty-six healthy male volunteers were enrolled in the study. Twenty-six subjects were dosed period I, and all 26 subjects successfully completed the entire clinical portion of the study.

Selection criteria: Selection criteria include male volunteers between the age of 18 and 45 years with physical examination and medical history within normal limits, body weight within ± 10% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983), and normal electrocardiogram. Physical exam, ECG and laboratory tests were conducted within 2 weeks of the study.

Laboratory tests: Blood chemistry, urine analysis, liver, HIV and kidney function tests were performed within 2 weeks of the study. Laboratory evaluations were not exceeded 10% of normal limits.

Exclusion criteria: Exclusion criteria were: ingestion of an investigational drug within four weeks prior to entry into the study; smoking tobacco; an acute illness or surgery during the four weeks prior to entry into the study; history of adverse reactions or allergy to aspirin, orphenadrine citrate, caffeine or related drugs; presence of significant renal, cardiac, hematopoietic, neurological, pulmonary or gastrointestinal pathology; presence of psychiatric disorders, glaucoma, diabetes or hyperthyroidism; any medications within fourteen days prior to the start of the study; ingestion of alcoholic beverage or caffeine or xanthine-containing food or beverages within 48 hours prior to start of the study.

Dose and treatment: All subjects completed an overnight fast. No meals were served within 4 hours of any of the following treatments:

A. Test product: 1 x 50 mg/770 mg/60 mg Orphenadrine Citrate, Aspirin and Caffeine Tablet (Invamed), lot #D950606, lot size tablets, content uniformity 103.8%, 96.1% and 102.7%, potency 102.6%, 98.4% and 100.3% for Orphenadrine, Aspirin and Caffeine, respectively.

B. Reference product: 1 x 50 mg/770 mg/60 mg Norgesic^{R} Tablet (3M pharmaceuticals), lot #G260, Exp. 9/97, content uniformity 99.0%, 100.4% and 99.5%, potency 99.7%, 99.3% and 101.0% for Orphenadrine, Aspirin and Caffeine, respectively.

Washout period: One week

Food and fluid intake: Subjects fasted for ten hours prior to dosing. Lunch was served four hours after dosing. Water (240 mL) was given with the dose. Water intake was not permitted from 1 hour prior to dose administration until 2 hours after dosing.

Blood samples: Blood samples were collected at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 60 hours. The plasma samples intended for orphenadrine analyses were stored frozen at -20°C until transferred to the laboratory.

Safety Evaluations: Blood pressure and heart rate were measured prior to dosing, at scheduled intervals after dosing and the discretion of the investigators.

Analytical Methodology

Statistical Analysis

Statistical analysis was performed on orphenadrine, salicylic acid and caffeine data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The data analyzed by ANOVA were also performed for blood drug concentrations at each sampling time. The 90% confidence intervals using the two one-sided t test method were calculated for AUC(0-t), AUCinf and Cmax for each analyte.

IV. In Vivo Results:

Twenty-six healthy male subjects were entered into the study. The study was successfully completed in all 26 subjects enrolled. Nineteen adverse events were reported in twelve of twenty-six subjects dosed and included the following events: dizziness (3), headache (7), hot flushes (1), left otitis externa (1), malaise (2), numerous abrasions (1), pharyngitis (1), purpura (2) and sweating increased (1). There were no serious adverse events or any events which required terminating any subject from the study.

The plasma levels and pharmacokinetic parameters for orphenadrine in twenty-six (N=26) are summarized below:

Table I

Mean Plasma Orphenadrine Concentrations and Pharmacokinetic Parameters Following a Single Dosing of 50 mg/770 mg/60 mg Orphenadrine Citrate, Aspirin and Caffeine (1 Tablet) Under Fasting Conditions (N=26)

Time hr	Invamed Test Product Lot#D950606 ng/mL (CV)	3M Reference Product Lot# G260 ng/mL (CV)
0	0.00	0.00
0.25	0.00 (.)	0.00 (.)
0.50	0.21 (510)	0.08 (510)
0.75	1.81 (189)	3.28 (193)
1	9.96 (101)	9.15 (102)
2.00	36.83 (36)	40.25 (45)
3	51.29 (22)	52.70 (28)
4	54.07 (26)	51.67 (26)
6	47.25 (29)	45.49 (29)
8	33.34 (27)	33.74 (29)
10	26.47 (32)	27.35 (34)
12	20.76 (32)	20.63 (31)
16	16.23 (39)	16.67 (42)
24	13.56 (38)	13.67 (39)
36	7.53 (45)	7.36 (49)
48	4.55 (61)	4.84 (77)
60	2.51 (94)	2.13 (99)
	Mean (CV)	Mean (CV)
AUC(0-t) ng.hr/mL	836.62(33.9)	837.33(36.8)
AUCinf ng.hr/mL	933.33(34.1)	929.61(36.8)
CMAX (ng/mL)	56.98(22.8)	55.60(25.3)
Kel (1/hr)	0.042	0.044
Half (hr)	17.18	16.61
Tmax(hr)	3.81	3.50

	90% CI
LnAUC(0-t)	96.0-105.0%
LnAUCi	96.6-105.0%
LnCmax	95.9-110.0%

Plasma Orphenadrine:

1. The orphenadrine plasma levels peaked at 3 and 4 hours for the reference and the test products, respectively. The levels within

each drug were similar. There were no statistically significant differences between the plasma orphenadrine levels at all sampling time points.

2. The data demonstrate that there are no statistically significant differences for orphenadrine between the test and the reference product for AUC(0-t), AUCi and Cmax. Differences from the least squares reference means of -0.08%, 0.42% and 2.4% for orphenadrine AUC(0-t), AUCi and Cmax, respectively, were observed. The 90% confidence intervals for each of the above parameter are within the acceptable range of 80-125%. The reviewer's calculations are same as those submitted by the firm.

Formulations:

Invamed's formulations for its Orphenadrine Citrate, Aspirin and Caffeine 50 mg/770 mg/60 mg and 25 mg/385 mg/30 mg Tablets are shown below:

Component	Invagesic **25/385/30 mg MG Per Tablet**	Invagesic Forte **50/770/60 mg MG Per Tablet**
(Green Layer)		
Orphenadrine Citrate, USP	25.0	50.0
Caffeine, USP	30.0	60.0
Lactose Monohydrate, NF 18		
Lake Blend Green		
Povidone, USP		
Croscarmellose Sodium, NF 18		
Purified Water, USP 23*		
Lactose Monohydrate, NF 18		
Silicon Dioxide, NF 18		
Magnesium Stearate , NF 18		
(White Layer)		
Aspirin	428.0[1]	856.0[2]
Total	**664.00 Mg**	**1328.0 mg**

[1] Contains 385 mg Aspirin USP 23 per tablet
[2] Contains 770 mg Aspirin USP 23 per tablet
* Used in manufacturing process only. Does not appear in the final product.

In Vitro Dissolution Testing

Method: USP 23 apparatus 2 at 50 rpm
Medium: 900 mL of water
Sampling Time: 15, 30, 45 and 60 minutes
Number of Tablets: 12

Test Products: Invamed's Orphenadrine Citrate, Aspirin and Caffeine Tablets
50 mg/770 mg/60 mg, lot #D950606
25 mg/385 mg/30 mg , lot #D950605

Reference Products: 3M's Norgesic Tablets
50 mg/770 mg/60 mg, lot #G260
25 mg/385 mg/30 mg, lot #941144

The dissolution testing results are presented in Table II.

Comments:

1. The firm has submitted the plasma concentrations and pharmacokinetic parameters for aspirin (salicylic acid) and caffeine. Since Aspirin and Caffeine do not require bioequivalence testing based on the Agency memo dated May 4, 1995, and the fact that both products are AA rated, these data have not been reviewed.

2. For Orphenadrine, the firm's in vivo bioequivalence study under fasting conditions is acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions.

3. The 25 mg/385 mg/30 mg tablet is proportionally similar to the 50 mg/770 mg/60 mg tablet.

4. The firm's in vitro dissolution testing for its Orphenadrine Citrate, Aspirin and Caffeine, 25 mg/385 mg/30 mg and 50 mg/770 mg/60 mg tablets is acceptable.

Recommendations:

1. The single-dose bioequivalence study under fasting conditions conducted by Invamed Inc., on its Orphenadrine Citrate, Aspirin and Caffeine (Invagesic Forte) 50 mg/770 mg/60 mg Tablet, lot #D950606, comparing it to Norgesic® Forte 50 mg/770 mg/60 mg Tablet, manufactured by 3M Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Invamed's Orphenadrine Citrate, Aspirin and Caffeine Tablet, 50 mg/770 mg/60 mg is bioequivalent to the reference product, Norgesic® Forte Tablet, 50 mg/770 mg/ 60 mg, manufactured by 3M Pharmaceuticals.

2. The dissolution testing conducted by the firm on its Orphenadrine Citrate, Aspirin and Caffeine Tablets, 50 mg/770 mg/60 mg and 25 mg/385 mg/30 mg, lot #D950606 and #D950605, respectively, is acceptable. The formulation for the 25 mg/385 mg/30 mg strength is proportionally similar to the 50 mg/770

mg/30 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of in vivo bioequivalence study requirements for the 25 mg/385 mg/30 mg tablet of the test product is granted. The Division of Bioequivalence deems Orphenadrine Citrate, Aspirin and Caffeine tablets (Invagesic), 25 mg/385 mg/30 mg, manufactured by Invamed Inc., to be bioequivalent to Norgesic® Tablets, 25 mg/385 mg/30 mg, manufactured by 3M Pharmaceuticals.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

NLT in 45 minutes for Aspirin and Caffeine
NLT in 60 minutes for Orphenadrine Citrate

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Ramesh M. Mhatre Date: 5/22/96

Concur: _____ Date: 5/24/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/5-22-96 wp 74817SDW.D95
cc: ANDA#74-817 original, HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division File

Table II. In Vitro Dissolution Testing

Drug (Generic Name): Orphenadrine Citrate, Aspirin and Caffeine
Dose Strength: 50/770/60 mg and 25/385/30 mg
ANDA No.: 74-817
Firm: Invamed Inc.
Submission Date: December 26, 1995
File Name: 74817SDW.D95

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of Water
Specifications: NLT in 45 minutes (Aspirin/Caffeine), in 60 miutes (Orphenadrine).
Reference Drug: Norgesic
Assay Methodology:

II. Results of In Vitro Dissolution Testing: Aspirin

Sampling Times (Minutes)	Test Product Lot # D950605 Strength(mg) 25/385/30 mg			Reference Product Lot # 941144 Strength(mg) 25/385/30 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	71.3		3.2	71.0		7.7
30	81.7		1.9	87.9		5.3
45	87.2		2.1	87.4		3.6
60	89.9		1.8	87.7		3.2

Caffeine

Sampling Times (Minutes)	Test Product Lot # D950605 Strength(mg) 25/385/30			Reference Product Lot # 941144 Strength(mg) 25/385/30 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	88.6		4.7	38.3		39.8
30	92.7		2.1	70.8		17.7
45	94.1		2.9	88.9		8.0
60	94.7		3.0	97.3		3.3

Table II. In Vitro Dissolution Testing

Drug (Generic Name): Orphenadrine Citrate, Aspirin and Caffeine
Dose Strength: 50/770/60 mg and 25/385/30 mg
ANDA No.: 74-817
Firm: Invamed Inc.
Submission Date: December 26, 1995
File Name: 74817SDW.D95

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of Water
Specifications: NLT in 45 minutes (Aspirin/Caffeine), in 60 miutes (Orphenadrine).
Reference Drug: Norgesic
Assay Methodology:

II. Results of In Vitro Dissolution Testing: Aspirin

Sampling Times (Minutes)	Test Product Lot # D950605 Strength(mg) 25/385/30 mg			Reference Product Lot # 941144 Strength(mg) 25/385/30 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	71.3		3.2	71.0		7.7
30	81.7		1.9	87.9		5.3
45	87.2		2.1	87.4		3.6
60	89.9		1.8	87.7		3.2

Caffeine

Sampling Times (Minutes)	Test Product Lot # D950605 Strength(mg) 25/385/30			Reference Product Lot # 941144 Strength(mg) 25/385/30 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	88.6		4.7	38.3		39.8
30	92.7		2.1	70.8		17.7
45	94.1		2.9	88.9		8.0
60	94.7		3.0	97.3		3.3

II. Results of In Vitro Dissolution Testing: Orphenadrine Citrate

Sampling Times (Minutes)	Test Product Lot # D950605 Strength(mg) 25/385/30			Reference Product Lot # 941144 Strength(mg) 25/385/30 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	89.5		4.9	36.5		42.4
30	93.3		1.9	70.4		18.3
45	94.8		3.1	89.1		8.1
60	95.5		3.0	97.8		3.5

II. Results of In Vitro Dissolution Testing: Aspirin

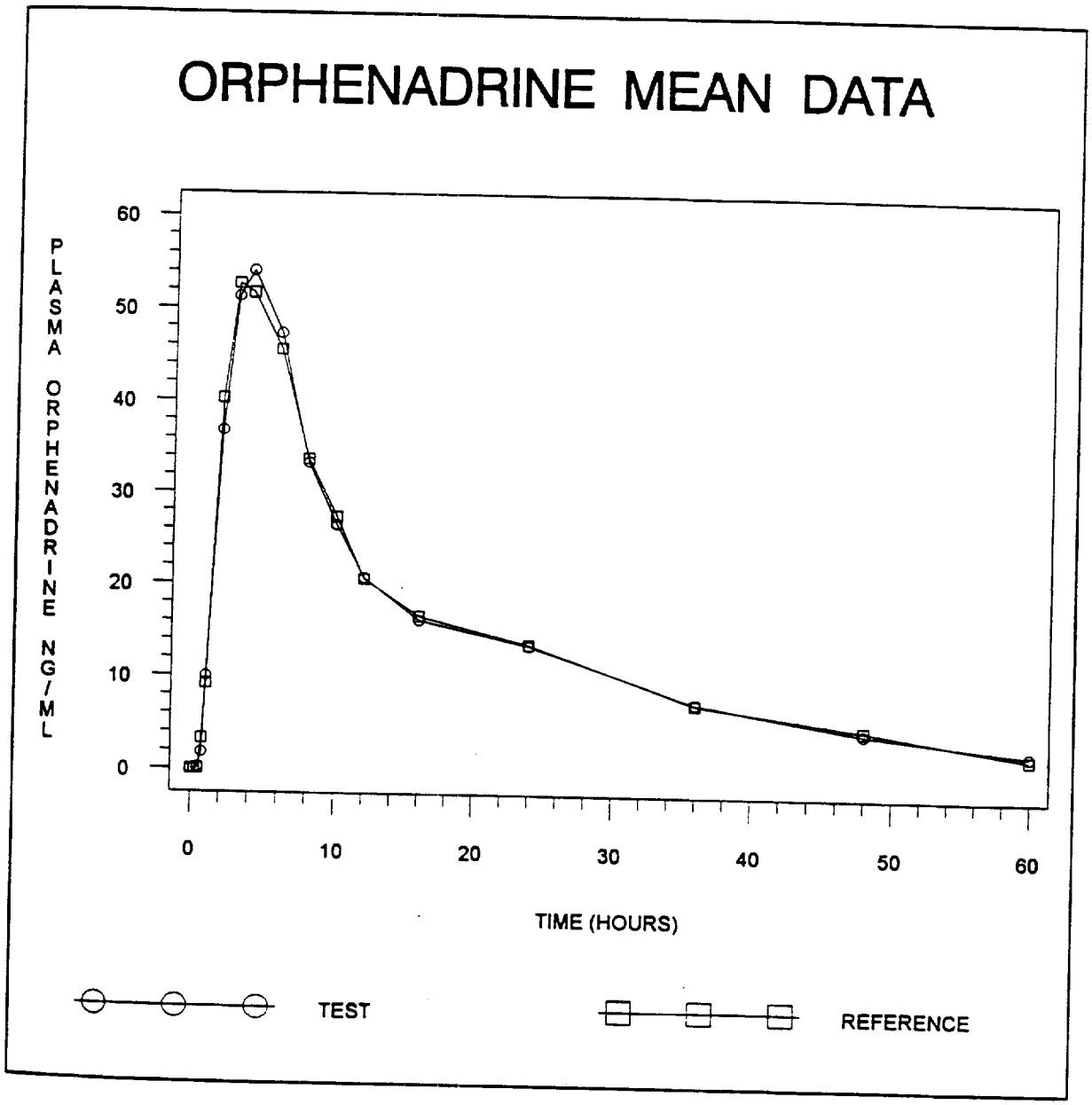
Sampling Times (Minutes)	Test Product Lot # D950606 Strength(mg) 50/770/60			Reference Product Lot # G260 Strength(mg) 50/770/60 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	71.8		6.5	68.1		8.1
30	80.5		5.6	79.9		6.3
45	84.5		5.2	85.9		5.8
60	87.0		4.3	88.6		4.3

II. Results of In Vitro Dissolution Testing: Caffeine

Sampling Times (Minutes)	Test Product Lot # D950606 Strength(mg) 50/770/60			Reference Product Lot # G260 Strength(mg) 50/770/60 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	93.7		9.7	70.0		31.5
30	98.9		5.3	87.2		16.0
45	101.5		3.1	96.4		8.6
60	103.0		2.8	99.7		5.9

II. Results of In Vitro Dissolution Testing: Orphenadrine Citrate						
Sampling Times (Minutes)	Test Product Lot # D950606 Strength(mg) 50/770/60			Reference Product Lot # G260 Strength(mg) 50/770/60 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	93.5		10.1	68.1		31.6
30	98.6		5.4	84.9		16.4
45	101.3		2.7	93.9		8.8
60	102.8		2.8	97.1		5.7

Figure 4.5.1 Linear Plot of Mean Plasma Orphenadrine Concentrations *vs* Time



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