CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 75141

Trade Name Orphengesic and Orphengesic Forte

Generic Name Orphenadrine Citrate 25mg, Aspirin 385mg and Caffine 30mg and Orphenadrine Citrate 50mg, Aspirin 770mg and Caffine 60mg

Sponsor Par Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 75141

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
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Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

x **CENTER FOR DRUG EVALUATION AND RESEARCH**

Application Number 75141

APPROVAL LETTER

HRD-205

ANDA 75-141

MAY 29 1998

Par Pharmaceuticals, Inc.
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

This is in reference to your abbreviated new drug application dated June 9, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Orphengesic™ (Orphenadrine Citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg) and Orphengesic Forte™ (Orphenadrine Citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg).

Reference is also made to your amendments dated January 30, March 31, April 20, May 13, May 19, and May 29, 1998.

We have completed the review of this abbreviated application and have concluded that the drugs are safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Orphengesic Tablets (Orphenadrine Citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg) and Orphengesic Forte Tablets (Orphenadrine Citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg) to be bioequivalent and, therefore, therapeutically equivalent to the listed drugs (Norgesic® and Norgesic® Forte Tablets, respectively of 3M Pharmaceuticals Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method 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 and 314.98. 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-40). 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 be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75141

FINAL PRINTED LABELING

NDC 49884-472-05

ORPHENGESIC TABLETS

(Orphenadrine Citrate, Aspirin, and Caffeine Tablets)

25 mg/385 mg/30 mg

Rx only

500 TABLETS

Each tablet contains:
Orphenadrine Citrate, USP ..... 25 mg
Aspirin, USP ..... 385 mg
Caffeine, USP ..... 30 mg

USUAL ADULT DOSAGE:
One or two tablets three to four times daily. See Accompanying Literature.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Pharmacists: This is a bulk package.
Dispense in a tight, light-resistant container.

Store below 30°C (86°F).

Control No.:

Exp. Date:

Tablet #472
I0398

Par Pharmaceutical, Inc.
Spring Valley, NY 10977

MAY 29 1998

N 3 49884-472-05 4

NDC 49884-473-05

ORPHENGESIC FORTE TABLETS

(Orphenadrine Citrate, Aspirin, and Caffeine Tablets)

50 mg/770 mg/60 mg

Rx only

500 TABLETS

Each tablet contains:
Orphenadrine Citrate, USP ..... 50 mg
Aspirin, USP ..... 770 mg
Caffeine, USP ..... 60 mg

USUAL ADULT DOSAGE:
One-half or one tablet three to four times daily. See Accompanying Literature.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Pharmacists: This is a bulk package.
Dispense in a tight, light-resistant container.

Store below 30°C (86°F).

Control No.:

Exp. Date:

Tablet #473
I0398

Par Pharmaceutical, Inc.
Spring Valley, NY 10977

N 3 49884-473-05 1

NDC 49884-472-01

ORPHENGESIC TABLETS

(Orphenadrine Citrate, Aspirin, and Caffeine Tablets)

25 mg/385 mg/30 mg

Rx only

100 TABLETS

Each tablet contains:
Orphenadrine Citrate, USP ..... 25 mg
Aspirin, USP ..... 385 mg
Caffeine, USP ..... 30 mg

USUAL ADULT DOSAGE:
One or two tablets three to four times daily. See Accompanying Literature.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Pharmacists: This is a bulk package.
Dispense in a tight, light-resistant container.

Store below 30°C (86°F).

Control No.:

Exp. Date:

Tablet #472
I0398

Par Pharmaceutical, Inc.
Spring Valley, NY 10977

MAY 29 1998

N 3 49884-472-01 6

NDC 49884-473-01

ORPHENGESIC FORTE TABLETS

(Orphenadrine Citrate, Aspirin, and Caffeine Tablets)

50 mg/770 mg/60 mg

Rx only

100 TABLETS

Each tablet contains:
Orphenadrine Citrate, USP ..... 50 mg
Aspirin, USP ..... 770 mg
Caffeine, USP ..... 60 mg

USUAL ADULT DOSAGE:
One-half or one tablet three to four times daily. See Accompanying Literature.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Pharmacists: This is a bulk package.
Dispense in a tight, light-resistant container.

Store below 30°C (86°F).

Control No.:

Exp. Date:

Tablet #473
I0398
Par Pharmaceutical, Inc.
Spring Valley, NY 10977

N 3 49884-473-01 3

010472-01

ORPHENGESIC
(Orphenadrine Citrate, Aspirin and Caffeine Tablets 25 mg/385 mg/30 mg)
AND
ORPHENGESIC FORTE TABLETS
(Orphenadrine Citrate, Aspirin and Caffeine Tablets 50 mg/770 mg/60 mg)

10398

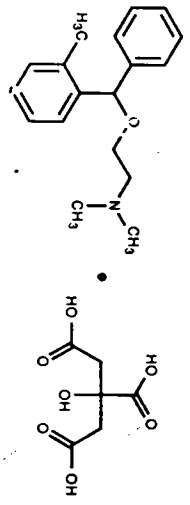
010472-01

DESCRIPTION

Each Orphengesic Tablet, for oral administration contains Orphenadrine Citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg. Each Orphengesic Forte Tablet, for oral administration contains Orphenadrine Citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg.

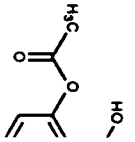
In addition, each tablet contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, D&C yellow #10, FD&C blue #1, povidone, pregelatinized starch, stearic acid, and zinc stearate.

Orphenadrine Citrate is (2-dimethylaminoethyl 2-methylbenzhydryl ether citrate). It is a white, practically odorless, crystalline powder, having a bitter taste. It is sparingly soluble in water; slightly soluble in alcohol. It has the following structural formula:



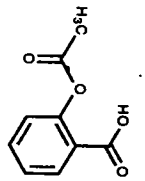
$C_{18}H_{23}NO \cdot C_6H_8O_7$ MW 461.51

Aspirin, salicylic acid acetate, is a non-opiate analgesic, anti-inflammatory and antipyretic agent. It occurs as a white, crystalline tabular or needle-like powder and is odorless or has a faint odor. It is sparingly soluble in water, freely soluble in alcohol and chloroform. It has the following structural formula:



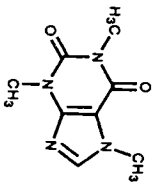
$C_{18}H_{23}NO-C_6H_8O_7$ MW 461.51

Aspirin, salicylic acid acetate, is a non-opiate analgesic, anti-inflammatory and antipyretic agent. It occurs as a white, crystalline tabular or needle-like powder and is odorless or has a faint odor. It is sparingly soluble in water, freely soluble in alcohol and chloroform. It has the following structural formula:



$C_9H_8O_4$ MW 180.16

Caffeine is a central nervous system stimulant which occurs as a white powder or white glistening needles, usually matted together. It is sparingly soluble in alcohol, and freely soluble in chloroform. The chemical name for caffeine is, 1,3,7-Trimethylxanthine. It has the following structural formula:



$C_8H_{10}N_4O_2$ MW 194.19

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 Orphenadrine Citrate, Aspirin and Caffeine 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.

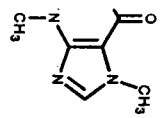
The mode of therapeutic action of orphenadrine has not been clearly identified, but may be related to its analgesic properties. Orphenadrine citrate also possesses anti-cholinergic actions.

INDICATIONS AND USAGE

Orphengesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) and Orphengesic 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. Orphengesic Tablets and Orphengesic Forte



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

INDICATIONS AND USAGE

Orphengesic (Orphenadrine Citrate, Aspirin and Caffeine 25 mg/385 mg/30 mg) and Orphengesic 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. Orphengesic Tablets and Orphengesic Forte Tablets do not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Because of the mild anticholinergic effect of orphenadrine, Orphengesic Tablets or Orphengesic Forte Tablets

should not be used in patients with glaucoma, pyloric or duodenal obstruction, achalasia, prostatic hypertrophy or obstructions at the bladder neck. Orphengesic Tablets or Orphengesic Forte 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. Orphengesic Tablets (Orphenadrine Citrate, Aspirin and Caffeine Tablets 25 mg/385 mg/30 mg) and Orphengesic Forte Tablets (Orphenadrine Citrate, Aspirin and Caffeine Tablets 50 mg/770 mg/60 mg) contain aspirin and therefore are not recommended for use in patients with chicken pox, influenza, or flu symptoms.

Orphengesic Tablets and Orphengesic Forte Tablets 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 its possible 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 Orphengesic Tablets and Orphengesic Forte Tablets has not been established; therefore, if Orphengesic Tablets or Orphengesic Forte Tablets are prescribed for prolonged use, periodic monitoring of blood, urine and liver function values is recommended.

ADVERSE REACTIONS

Side effects of Orphengesic Tablets or Orphengesic Forte 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. Infre-

ing of blood, urine and liver function values is recommended.

ADVERSE REACTIONS

Side effects of Orphengesic Tablets or Orphengesic Forte 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 orphenadrine citrate, aspirin and caffeine has been reported. No causal relationship has been established. Rare G.I. hemorrhage due to aspirin content may be associated with the administration of Orphengesic Tablets or Orphengesic Forte Tablets. Some patients may experience transient episodes of light-headedness, dizziness or syncope.

DOSAGE AND ADMINISTRATION

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

Orphengesic Forte: Adults 1/2 to 1 tablet 3 to 4 times daily.

HOW SUPPLIED

Orphengesic Tablets (Orphenadrine Citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg): Two-layered white/green, round, unscored, flat faced, beveled-edge tablets debossed "3M" over "472" on the white side and plain on the green side are available in bottles of 100 tablets (NDC 49884-472-01) and 500 tablets (NDC 49884-472-05).

Orphengesic Forte Tablets (Orphenadrine Citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg): Two-layered, white/green capsule shaped tablets debossed "3M" and "473" with bisect on the white side and plain on the green side are available in bottles of 100 tablets (NDC 49884-473-01) and 500 tablets (NDC 49884-473-05).

Store below 30°C (86°F).

Rx only

Manufactured by:
PAR PHARMACEUTICAL, INC.
Spring Valley, NY 10977

Issued: 03/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75141

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. Three (3)

2. ANDA # 75141

3. NAME AND ADDRESS OF APPLICANT
Par Pharmaceutical, Inc.,
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road,
Spring Valley, NY 10977

4. LEGAL BASIS FOR SUBMISSION
There are no patent or exclusivity issues associated with the reference listed drug, Norgesic™ (3M Pharmaceuticals).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME

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

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

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

9. AMENDMENTS AND OTHER DATES:
Fax amendment: March 31, 1998
Telephone amendment: May 13, 1998
Telephone amendment: May 19, 1998

10. PHARMACOLOGICAL CATEGORY
Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

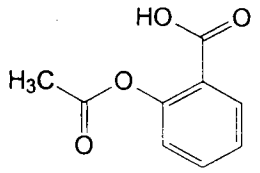
DMF#	Type/Product	DMF Holder	LOA

13. DOSAGE FORM
Tablets

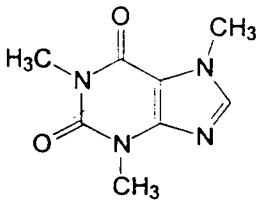
14. POTENCY
Orphengesic Tablets (Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg)
Orphengesic Forte Tablets (Orphenadrine citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg)

15. CHEMICAL NAME AND STRUCTURE

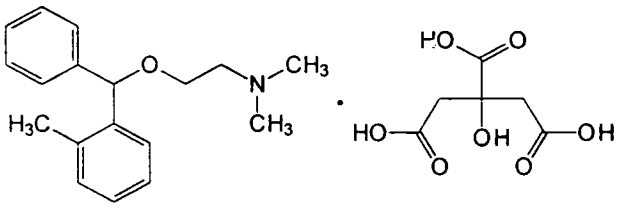
Aspirin. Benzoic acid, 2-(acetyloxy)-. $C_9H_8O_4$. 180.16. 50-78-2. Analgestic, antipyretic, antirheumatic. USP 23, page 131.



Caffeine. 1*H*-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl-. $C_8H_{10}N_4O_2$. 194.19. 58-08-2. Stimulant (central). USP 23, page 241.



phenadrine Citrate. Ethanamine, *N,N*-dimethyl-2-[(2-methylphenyl)phenyl-methoxt]-, (±)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1). $C_{18}H_{23}NO \bullet C_6H_8O_7$. 461.51. 4682-36-4. Relaxant (skeletal muscle); antihistaminic. USP 23, page 1116.



16. RECORDS AND REPORTS
N/A

17. COMMENTS

This application (ANDA 75141) is approvable.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is now approvable.

19. REVIEWER: Liang-Lii Huang, Ph.D.
DATE COMPLETED: May 19, 1998

Endorsements:

HFD-627/Liang-Lii Huang, Ph.D./5-19-98
HFD-627/Paul Schwartz, Ph.D./5-19-98 5/21/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75141

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #75-141 **SPONSOR:** Par Pharmaceutical, Inc.
DRUGS: Orphenadrine Citrate/Aspirin/Caffeine (Orphengesic Forte)
Orphenadrine Citrate/Aspirin/Caffeine (Orphengesic)
DOSAGE FORM: Tablets
STRENGTHS: 50mg/770mg/60mg and 25mg/385mg/30mg
TYPE OF STUDY: Single-dose, Fasting
CLINICAL SITE:
ANALYTICAL SI

STUDY SUMMARY:
The single-dose bioequivalence study conducted under fasting conditions on Orphenadrine Citrate/Aspirin/Caffeine, 50mg/770mg/60mg Tablets (Orphengesic Forte) was found acceptable by the Division of Bioequivalence. The plasma samples were analyzed for Orphenadrine levels.

DISSOLUTION:
The dissolution testing for each strength was found acceptable.

WAIVER REQUEST:
The waiver of bioequivalence study was granted for the lower strength of the test product, Orphenadrine Citrate/Aspirin/Caffeine, 25mg/385mg/30mg Tablets (Orphengesic).

PRIMARY REVIEWER: F. Nouravarsani **BRANCH:** III

SIGNITURE: **DATE:** 5/8/98

Acting Team Leader: M. Makary **BRANCH:** III

SIGNITURE: **DATE:** 5/8/98

DIRECTOR: Dale P. Conner
DIVISION OF BIOEQUIVALENCE:

SIGNITURE: **DATE:** 5/11/98

DIRECTOR: Doug Sporn
OFFICE OF GENERIC DRUGS:

SIGNITURE: **DATE:**

Aspirin/Caffeine/**Orphenadrine Citrate**
Orphengesic Forte Tablets
770 mg/60 mg/50 mg
Orphengesic Tablets
385 mg/30 mg/25 mg
ANDA #75-141
Reviewer: F. Nouravarsani
75141SDA.198

Par Pharmaceutical, Inc.
Spring Valley, NY
Submission Date:
January 30, 1998
April 20, 1998

Review of Bioequivalence Study Amendments, Dissolution Testing, Waiver Request, and Recommendations for Approval

Par Pharmaceutical, Inc. had previously submitted a single-dose bioequivalence study conducted under fasting conditions and dissolution testing on its test product, Orphengesic Forte Tablets (Orphenadrine Citrate/Aspirin/Caffeine, 50mg/770mg/60mg) and the listed reference product, NORGESIC FORTE Tablets (Orphenadrine Citrate/Aspirin/Caffeine, 50mg/770mg/60mg) manufactured by 3M Pharmaceuticals (NDA #13416 004, October 27, 1982).

The firm had also submitted dissolution testing data for its lower strength test product, Orphengesic Tablets (Orphenadrine Citrate/Aspirin/Caffeine, 25mg/385mg/30mg) and the reference product, NORGESIC Tablets (Orphenadrine Citrate/Aspirin/Caffeine, 25mg/385mg/30mg), and had requested for a waiver of bio-study requirements.

In the current submissions the firm has responded to the DBE deficiencies letter and phone call as it follows:

Deficiency #1:

The firm was requested to clarify the difference between and to report the in the 'Method Validation'.

PAGES 2-4 METHODS and CMC

The firm has submitted the raw data for each rejected run in its submission dated April 20, 1998.

The response is acceptable.

Deficiency #4:

The firm had submitted dissolution testing data conducted on 12 units of each strength of the test and reference products in 900 mL water using apparatus 1 (basket) at 75 rpm on June 09, 1997.

The firm was requested to submit dissolution testing data conducted on 12 units of each strength of the test and reference products in 900 mL of water (37° C) using the USP apparatus 2 (paddle) at 50 rpm. The sampling times were requested to be at 15, 30, 45, and 60 minutes.

Response to Deficiency #4:

The firm submitted dissolution testing data using the conditions requested by the Division. The data are shown in Tables 1 and 2.

The firm stated that the previously submitted dissolution testing data using apparatus 1 (basket) at 75 rpm was based on method used by the innovator drug company, 3M Pharmaceuticals, with specifications of 70% at 45 minutes for each component. The firm included in its current submission a copy of the letter from 3M to Par (dated September 5, 1995) regarding the dissolution testing method and specifications of the reference products.

Reviewer Comments to Deficiency #4:

a) The method and specifications used by 3M Pharmaceuticals were confirmed by E-Mail from Dr. John Lazor (OCPB) to Dr. Nhan Tran (DBE) on March 22, 1998 (Attachment One).

Results of the dissolution testing data submitted previously on June 09, 1997 meet the specifications of 'Not Less Than 70% at 45 minutes' for each component of both strengths of the test and reference products (Tables 3 and 4).

c) There is no dissolution testing method listed in the current USP 23 (1995) and its supplements #1-7 for Orphenadrine Citrate/Aspirin/Caffeine Tablets.

Waiver Request of Bioequivalence Study for Orphengesic Tablets (Orphenadrine Citrate/Aspirin/Caffeine, 25mg/385mg/30mg):

The firm had requested a waiver of bioequivalence study requirements for its test product, Orphengesic Tablets (Orphenadrine Citrate/Aspirin/Caffeine, 25mg/385mg/30mg) based on the following:

(a) The comparative single-dose bioequivalence study conducted on the Orphengesic Forte Tablets (Orphenadrine Citrate/Aspirin/ Caffeine, 50mg/770mg/60mg) Tablets, and NORGESIC FORTE Tablets.

(b) The proportional similarity of the formulations of the lower and higher strengths of the test product.

(c) The comparative dissolution testing conducted on the lower and higher strengths of the test and reference products.

Deficiency of the Current Submission: None.

Recommendations:

1. The single-dose bioequivalence study conducted under fasting conditions by Par Pharmaceutical, Inc. on its Orphengesic Forte Tablets (Orphenadrine Citrate/Aspirin/Caffeine, 50 mg/770 mg/60 mg), lot #SB0086, comparing it to NORGESIC FORTE Tablets (Orphenadrine Citrate/Aspirin/Caffeine, 50 mg/770 mg/60 mg), lot #931653, has been found acceptable by the Division of Bioequivalence.

The study demonstrates that Par's Orphenadrine Citrate/Aspirin/ Caffeine, 50 mg/770 mg/60 mg is bioequivalent to the reference

product, NORGESIC FORTE Tablets (Orphenadrine Citrate/Aspirin/ Caffeine, 50 mg/770 mg/60 mg) manufactured by 3M Pharmaceuticals.

2. The dissolution testing conducted by Par Pharmaceutical, Inc. on its Orphengesic Forte Tablets (Orphenadrine Citrate/Aspirin/ Caffeine, 50 mg/770 mg/60 mg), lot #SB0086, and Orphengesic Tablets (Orphenadrine Citrate/Aspirin/Caffeine, 25 mg/385 mg/30 mg), lot #SB0078, has been found acceptable.

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 1 (basket) at 75 rpm. The test product should meet the following specifications:

> Not less than 70% of the labeled amount of each component in the dosage form is dissolved in 45 minutes.

4. The dissolution testing conducted by Par Pharmaceutical, Inc. on its Orphenadrine Citrate/Aspirin/Caffeine, 25 mg/385 mg/30 mg Tablets (lot #SB0078) is acceptable. The firm has conducted an acceptable in-vivo bioequivalence study comparing its higher strength test product with the reference product, NORGESIC FORTE Tablets manufactured by 3M Pharmaceuticals. The formulation for the lower strength is proportionally similar to the higher strength of the test product which underwent bioequivalency testing. The waiver of in-vivo bioequivalence study requirements for the Orphenadrine Citrate/Aspirin/Caffeine, 25 mg/385 mg/30 mg Tablets is granted

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED MMAKARY
FT INITIALED MMAKARY

Concur:_____ Date: 5/11/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

FNouravarsani/05-07-98/WP:75141SDA.198

Table 1: In Vitro Dissolution Testing

Drug (Generic Name): Orphengesic Forte (Orphenadrine Citrate/ Aspirin/Caffeine) Tablets
Dose Strength: 50 mg/770 mg/60 mg
ANDA: #75-141
Firm: Par Pharmaceutical, Inc.
Submission Date: January 30, 1998

I. Conditions for Dissolution Testing:

USP XXIII Basket ___ Paddle X RPM 50 No. Units Tested 12

Medium: water at 37° C Volume: 900 mL

Reference Drug: Norgesic Forte Tablets

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

A: Orphenadrine Citrate

Sampling Times minutes	Test Product: Lot #SB0086 Strength (mg) 50			Reference Product: Lot #931653 Strength (mg) 50		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	29.9		(32.5)	69.1		(29.7)
30	69.9		(25.4)	82.3		(17.3)
45	97.5		(1.2)	87.0		(10.8)
60	99.2		(0.9)	91.6		(5.2)

B: Aspirin

Sampling Times minutes	Test Product: Lot #SB0086 Strength (mg) 770			Reference Product: Lot #931653 Strength (mg) 770		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	77.2		(7.1)	75.0		(4.4)
30	92.8		(2.8)	85.7		(3.9)
45	96.2		(2.4)	90.5		(3.1)
60	96.4		(1.9)	94.1		(2.9)

C: Caffeine

Sampling Times minutes	Test Product: Lot #SB0086 Strength (mg) 60			Reference Product: Lot #931653 Strength (mg) 60		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	30.4		(33.0)	70.1		(29.4)
30	70.1		(25.8)	83.6		(16.7)
45	97.0		(2.1)	88.8		(10.1)
60	98.8		(1.9)	93.8		(5.3)

Table 2: In Vitro Dissolution Testing

Drug (Generic Name): Orphengesic (Orphenadrine Citrate/ Aspirin/Caffeine) Tablets
Dose Strength: 25 mg/385 mg/30 mg
ANDA: #75-141
Firm: Par Pharmaceutical, Inc.
Submission Date: January 30, 1998

I. Conditions for Dissolution Testing:

USP XXIII Basket ___ Paddle X RPM 50 No. Units Tested 12

Medium: water at 37° C Volume: 900 mL

Reference Drug: Norgesic Tablets

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

A: Orphenadrine Citrate

Sampling Times minutes	Test Product: Lot #SB0078 Strength (mg) 25			Reference Product: Lot #930214 Strength (mg) 25		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	48.8		(32.9)	58.1		(26.7)
30	92.1		(12.1)	82.3		(17.6)
45	99.6		(1.2)	91.4		(11.8)
60	100.5		(0.7)	97.5		(7.6)

B: Aspirin

Sampling Times minutes	Test Product: Lot #SB0078 Strength (mg) 385			Reference Product: Lot #930214 Strength (mg) 385		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	73.1		(5.5)	68.2		(7.2)
30	89.1		(3.7)	79.2		(3.9)
45	92.5		(2.9)	82.5		(5.0)
60	94.1		(2.1)	84.5		4.5)

C: Caffeine

Sampling Times minutes	Test Product: Lot #SB0078 Strength (mg) 30			Reference Product: Lot #930214 Strength (mg) 30		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	50.2		(33.6)	52.7		(25.7)
30	91.9		(12.8)	81.2		(16.8)
45	99.0		(2.7)	90.0		(11.2)
60	100.6		(2.2)	94.3		(7.0)

Table 3: In Vitro Dissolution Testing

Drug (Generic Name): Orphengesic Forte (Orphenadrine Citrate/ Aspirin/Caffeine) Tablets
Dose Strength: 50 mg/770 mg/60 mg
ANDA: #75-141
Firm: Par Pharmaceutical, Inc.
Submission Date: June 09, 1997

I. Conditions for Dissolution Testing:

USP XXIII Basket X Paddle ___ RPM 75 No. Units Tested 12

Medium: water at 37° C Volume: 900 mL

Reference Drug: Norgesic Forte Tablets

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

A: Orphenadrine Citrate

Sampling Times minutes	Test Product: Lot #SB0086 Strength (mg) 50			Reference Product: Lot #931653 Strength (mg) 50		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	73.7	.	(12.4)	88.9	.	(6.7)
30	99.5	.	(0.9)	96.3	.	(4.4)
45	99.7	.	(1.0)	96.0	.	(4.2)
60	100.0		(1.0)	96.8		(4.6)

B: Aspirin

Sampling Times minutes	Test Product: Lot #SB0086 Strength (mg) 770			Reference Product: Lot #931653 Strength (mg) 770		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	47.7		(25.3)	70.1		(10.2)
30	86.3		(13.4)	92.3		(3.3)
45	94.2		(8.3)	97.8		(2.7)
60	95.4		(5.4)	98.2		(1.9)

C: Caffeine

Sampling Times minutes	Test Product: Lot #SB0086 Strength (mg) 60			Reference Product: Lot #931653 Strength (mg) 60		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	74.8		(11.3)	89.6		(8.2)
30	98.8		1.9)	96.2		(4.3)
45	99.7		1.6)	96.6		(3.9)
60	99.6		(1.7)	96.9		(4.6)

Table 4: In Vitro Dissolution Testing

Drug (Generic Name): Orphengesic (Orphenadrine Citrate/ Aspirin/Caffeine) Tablets
Dose Strength: 25 mg/385 mg/30 mg
ANDA: #75-141
Firm: Par Pharmaceutical, Inc.
Submission Date: June 09, 1997

I. Conditions for Dissolution Testing:

USP XXIII Basket X Paddle ___ RPM 75 No. Units Tested 12

Medium: water at 37° C Volume: 900 mL

Reference Drug: Norgesic Tablets

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

A: Orphenadrine Citrate

Sampling Times minutes	Test Product: Lot #SB0078 Strength (mg) 25			Reference Product: Lot #930214 Strength (mg) 25		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	77.7		(15.6)	74.5		(11.2)
30	97.2		(2.7)	101.0		(2.1)
45	98.9		(1.8)	101.3		(1.5)
60	99.0		(2.1)	101.5		(1.5)

B: Aspirin

Sampling Times minutes	Test Product: Lot #SB0078 Strength (mg) 385			Reference Product: Lot #930214 Strength (mg) 385		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	80.0		(8.9)	76.1		(9.2)
30	95.5		(1.7)	89.3		(7.4)
45	96.5		(0.9)	91.0		(6.3)
60	95.6		(1.5)	91.3		(7.5)

C: Caffeine

Sampling Times minutes	Test Product: Lot #SB0078 Strength (mg) 30			Reference Product: Lot #930214 Strength (mg) 30		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	79.8		(12.2)	75.9		(11.1)
30	99.0		(3.1)	101.7		(2.0)
45	99.6		(2.2)	101.2		(2.2)
60	98.9		(2.7)	101.6		(1.5)

Attachment one

E L E C T R O N I C M A I L M E S S A G E

ensitivity: COMPANY CONFIDENTIAL

Date: 22-Mar-1998 10:51pm EST
From: John Lazor
LAZOR
Dept: HFD-880 CRP2 N108
Tel No: 301-827-2005 FAX 301-827-257

O: Nhan Tran (TRAN)

ubject: Norgesic Forte

an Wang and Dennis Bashaw did some investigating into the dissolution
f Norgesic Forte Tablets.

er a 1993 letter to the company, their proposal was accepted. A review
y Dennis Bashaw in 1993 indicated that the Q was 75%, however he
ndicates that was in error. He accepted the company's proposal of 70%.
e will be writing a memo to the NDA to clarify this.

ne method and specification are:

Apparatus I (Basket)
mL water at 75RPM
LT (Q) 70% at 45 min for all three components.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-141 APPLICANT: Par Pharmaceutical, Inc.

DRUG PRODUCT: Orphengesic Forte Tablets (Orphenadrine Citrate/ Aspirin/Caffeine, 50mg/770mg/60mg)
and
Orphengesic Tablets (Orphenadrine Citrate/ Aspirin/Caffeine, 25mg/385mg/30mg)

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

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 Apparatus 1 (basket) at 75 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of each component in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: **ANDA 75-141**
ANDA DUPLICATE
DIVISION FILE
HFD-650/Bio Drug File
HFD-658/F. Nouravarsani

X:\NEW\FIRMSNZ\PAR\ltrs&rev\75141SDA.198
Printed in final on 5/8/98

Endorsements: (Final with Dates)
HFD-658/ F. Nouravarsani, 5/8/98
HFD-658/ M. Makary 5/8/98
HFD-650/ D. Conner 5/4/98

BIOEQUIVALENCY - ACCEPTABLE submission date: January 30, 1998 and April 20, 1998

1. **DISSOLUTION DATA** (DIS) 1-30-98
All Strengths: 50mg/770mg/60mg 25mg/385mg/30mg
Outcome: **AC**

2. **STUDY AMENDMENT** (STA) 1-30-98
Strength: 50mg/770mg/60mg
Outcome: AC

3. ~~**WAIVER (WAI)**~~ STA 2-98 ~~1-30-98~~
Strength: 25mg/385mg/30mg, 50mg/770/60mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments: The study amendment and dissolution testing were found acceptable. The waiver of bio-study for the lower strength was granted.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75141

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 75-141

DRUG PRODUCT: Orphengesic Tablets (Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg)
Orphengesic Forte Tablets (Orphenadrine citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg)

FIRM: Par Pharmaceutical, Inc.

DOSAGE FORM: Tablets

STRENGTH: Orphengesic Tablets (Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg)
Orphengesic Forte Tablets (Orphenadrine citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg)

CGMP: Statement/EIR Update Status:

An EER was found to be acceptable (12/22/97).

BIO: The single-dose Bioequivalence study conducted under fasting conditions on Orphenadrine citrate/aspirin/caffeine, 50mg/770mg/60mg tablets (Orphengesic Forte) was found acceptable by the div. of Bioequivalence. The waiver of bioequivalence study was granted for the lower strength of the test product, Orphenadrine citrate/aspirin/caffeine, 25mg/385mg/30mg tablets (Orphengesic) (reviewed by F. Nouravarsani, 5/8/98).

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Method validation was completed by the FDA Northeast Regional Laboratory (New York) and found to be satisfactory (12/22/97).

STABILITY: (Are containers used in study identical to those in container section?)

The containers used in the stability study are identical to those described in the container section.

LABELING:

Container, carton and insert labeling have been found satisfactory (Labeling approval summary 3/31/98, reviewed by C. Holquist)

STERILIZATION VALIDATION (IF APPLICABLE):

Not applicable

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

The tablets of the exhibit batch of the Orphengesic Tablets (Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg)(lot#SB0078) and the tablets of the Orphengesic Forte Tablets (Orphenadrine citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg)(lot#SB0086) were manufactured.

was found to be adequate (2/13/98, reviewed by Liang-Lii Huang, Ph.D.)

was found to be adequate (9/19/97, reviewed by MLS).

was found adequate (reviewed by R. Rajagopalan, 1/20/98)

SIZE OF STABILITY BATCHES- (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The exhibit batches (lot#SB0078 and SB0086) were the stability batches.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

The proposed production batch are tablets for the Orphengesic Tablets (Orphenadrine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg) and tablets for the Orphengesic Forte Tablets (Orphenadrine citrate 50 mg, Aspirin 770 mg and Caffeine 60 mg). The manufacturing process will be the same as was used for the exhibit batch.

CHEMIST: Liang-Lii Huang, Ph.D. **DATE:** May 19, 1998
SUPERVISOR: Paul Schwartz, Ph.D. **DATE:** May 19, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75141

CORRESPONDENCE

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

NEW CORRESP

1C

Copy 1✓
Copy 2
Copy 3 (field)*

May 19, 1998

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA 75-141 **TELEPHONE AMENDMENT**
Orphengesic Tablets
(Orphenadrine Citrate, Aspirin and Caffeine Tablets 25 mg/385 mg/60 mg
Orphengesic Forte Tablets
(Orphenadrine Citrate, Aspirin and Caffeine Tablets 50 mg/770 mg/60 mg

Dear Sir:

Reference is made to our telephone conversation with the Agency on Monday, May 18. 1998 regarding typographical errors contained on the quantitative statements found on pages 1185 and 1186 of our original application.

Enclosed please find revised quantitative statements of the composition of the drug product for Orphengesic and Orphengesic Forte Tablets. The statements were revised to reflect the correct Subtotal of Parts I - VI and Total of Parts I - VII .o·

Par Pharmaceutical, Inc., certifies that a field copy of this telephone amendment has been provided to the FDA Brooklyn. District Office. Please contact us if additional information is required.

Sincerely,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala

Michelle Bonomi-Huvala
Associate Director, Regulatory Affairs/R&D

Enclosures

cc: Brenda Holmes, District Director
Food and Drug Administration
Brooklyn District Office
850 Third Avenue
Brooklyn, New York 11232-1593

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MAY 20 199

GENERIC DRUGS

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

BIOAVAILABILITY

ORIG AMENDMENT

N/AP NAS
rechanneled
5/22/98

May 13, 1998

Copy 1 ✓
Copy 2

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA 75-141 **TELEPHONE AMENDMENT**
Orphengesic Tablets
(Orphenadrine Citrate, Aspirin and Caffeine Tablets 25 mg/385 mg/30 mg
Orphengesic Forte Tablets
(Orphenadrine Citrate, Aspirin and Caffeine Tablets 50 mg/770 mg/60 mg

Dear Sir:

We acknowledge receipt of the Agency's facsimile today outlining dissolution requirements for Orphengesic and Orphengesic Forte Tablets. We enclose a copy of the facsimile for your immediate reference.

Par Pharmaceutical, Inc., commits to incorporate the following dissolution testing and specification recommended by the Division of Bioequivalence into our stability and quality control program. The dissolution testing and associated specification will be incorporated prior to the manufacture of any batches marketed.

> Dissolution testing conducted in 900 mL of water at 37°C using USP Apparatus 1 (basket) at 75 rpm.
>
> Not less than , of the labeled amount of each component in the dosage form is dissolved in 45 minutes.

Par Pharmaceutical, Inc., also acknowledges that the Division of Bioequivalence has completed its review and has no further questions at this time.

We trust the response is adequate to approve ANDA 75-141 as amended. Please contact us if additional information is required.

Sincerely,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala

Michelle Bonomi- Huvala
Associate Director, Regulatory Affairs/R&D

RECEIVED
MAY 18 1998
GENERIC DRUGS

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

FPL
NDA DRUG AMENDMENT

N/FA

✓Copy 1
Copy 2
Copy 3 (field)*

FPL satisfactory
C. Hulquist
4/6/98

March 31, 1998

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

FAX

RE: ANDA 75-141 **~~MINOR~~ AMENDMENT**
ORPHENGESIC TABLETS
(Orphenadrine Citrate, Aspirin and Caffeine Tablets 25 mg/385 mg/30 mg)
ORPHENGESIC FORTE TABLETS
(Orphenadrine Citrate, Aspirin and Caffeine Tablets 50 mg/ 770 mg/60 mg)

Dear Sir/Madam:

Reference is made to our abbreviated new drug application submitted June 9, 1997. Reference is also made to your enclosed facsimile dated March 6, 1998 (Attachment I) outlining minor chemistry and labeling deficiencies associated with the application and the amendment dated January 13, 1998.

In light of the foregoing we offer the following supporting documentation in response to the deficiencies.

Chemistry Deficiencies

Comment 1

Response #8 in the January 13, 1998 minor amendment mentioned that the Orphenadrine Citrate Tablets appears to be incorrect. Document #S-473-004 should be Orphengesic Forte Tablets.

RECEIVED
APR 0 2 1998
GENERIC DRUGS

Response 1

Orphenadrine Citrate Tablets noted in Response #8 of the January 3, 1998 Minor Amendment was a typographical error. The title should read Orphengesic Forte Tablets for Document #S-473-004 as you have stated in the above comment.

In addition to responding to the deficiencies presented above, Par Pharmaceutical, Inc., notes and acknowledges the following comments.

1. The bioequivalence review continues. Comments, if any, will be transmitted at a later date.

Labeling Deficiencies

Comment

Please revise your container labels and insert labeling, as instructed above, and submit final printed labels and labeling. To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a) (8) (iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Response

The container labels and insert labeling were revised according to Section 126 of the FDA Modernization Act. We enclosed twelve (12) final printed copies of each for your review. In addition, a side-by-side comparison of the final printed labeling with that of the amendment of January 13, 1998, with differences annotated and explained, is provided to facilitate the review of the labeling. The final printed container labels (Attachment IV), final inerts labeling (Attachment V) and side-by- side comparisons (Attachment VI) are enclosed.

This concludes our response to the agency's facsimile dated March 6, 1998. Please contact us if additional information is required.

Sincerely,
PAR PHARMACEUTICAL, INC.

Teresa Tung
Senior Regulatory Affairs Associate

Enclosed

* Brenda Holmes, District Director
Food and Drug Administration
Brooklyn District Office
850 Third Avenue
Brooklyn, NY 11232-1593