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 Caffeine 30mg and Orphenadrine Citrate 50mg, Aspirin 770mg and Caffeine 60mg

Sponsor  Par Pharmaceuticals, Inc.
# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION 75141

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75141

APPROVAL LETTER
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
ORPHENGESIC TABLETS
(Orphenadrine Citrate, Aspirin, and Caffeine Tablets)
25 mg/385 mg/30 mg
Rx only
500 TABLETS

ORPHENGESIC FORTE TABLETS
(Orphenadrine Citrate, Aspirin, and Caffeine Tablets)
50 mg/770 mg/60 mg
Rx only
500 TABLETS
ORPHENGESIC TABLETS
(Oxphenadrine Citrate, Aspirin, and Caffeine Tablets)
25 mg/385 mg/30 mg
Rx only
100 TABLETS

ORPHENGESIC FORTE TABLETS
(Oxphenadrine Citrate, Aspirin, and Caffeine Tablets)
50 mg/770 mg/60 mg
Rx only
100 TABLETS
DESCRIPTION
Each Oxyphedrine Tablet, for oral administration, contains Oxymetazoline Chloride 25 mg, Aspirin 335 mg and Caffeine 30 mg. Each Oxyphedrine Nasal Spray contains Oxymetazoline Chloride 50 mg, Aspirin 770 mg and Caffeine 62 mg.

In addition, each tablet contains the following inactive ingredients: crospovidone, croscarmellose sodium, colloidal silicon dioxide, yellow iron oxide, FD&C Blue #1, potassium hydroxide, saccharin, and sodium chloride.

Oxymetazoline Chloride is (2S,4S)-4-(3-methylphenylcarbamoyl)-2-methyl-1-phenyl-propan-1-one hydrochloride. 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:

![Structural formula for Oxymetazoline Chloride]

Aspirin, salicylic acid acetate, is a non-steroid anti-inflammatory agent. It occurs as a white, crystalline, bluish or needle-like powder and is efflorescent or has a bready odor. It is sparingly soluble in water, freely soluble in alcohol and chloroform. It has the following structural formula:

![Structural formula for Aspirin]
Caffeine is a central nervous system stimulant which occurs as a white powder or white glancing needles, usually mixed 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:

**Chemical Structure of Caffeine**

CLINICAL PHARMACOLOGY

Dopamine is a neurotransmitter that plays a role in the reward system, neurological functions of the mesocortical system. Dopamine has been shown to produce hyperactive behaviors, which are not typically associated with excessive dopamine release. Dopamine plays a role in the reward system, where it is released in response to rewarding stimuli. The release of dopamine from the reward system is associated with the pleasure of eating food, sex, and other rewarding experiences. Dopamine is also involved in the regulation of movement, where it is necessary for the smooth and coordinated movement of the body. Dopamine is released in the basal ganglia, a region of the brain that plays a role in the regulation of movement. Dopamine is also involved in the regulation of mood, where it is necessary for the regulation of emotions. Dopamine is released in the ventral tegmental area, a region of the brain that is involved in the regulation of mood. Dopamine is also involved in the regulation of learning and memory, where it is necessary for the formation of new memories. Dopamine is released in the prefrontal cortex, a region of the brain that is involved in the regulation of learning and memory. Dopamine is also involved in the regulation of alertness, where it is necessary for the regulation of wakefulness. Dopamine is released in the anterior cingulate cortex, a region of the brain that is involved in the regulation of alertness.
CLINICAL PHARMACOLOGY

Orphenadrine citrate is a centrally acting (theta site) com-
pound which in general selectively bonds to locatory func-
tions of the reticular formation. Orphenadrine does not pro-
duce respiratory block, nor does it affect extraocular reflexes. Orphenadrine pre-
vents nicotine-induced convul-
sions 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 re-
lated to its analgesic properties. Orphenadrine citrate also pos-
sesses anti-cholinergic actions.

INDICATIONS AND USAGE

Orphenadrine Citrate, Aspirin and Caffeine 50 mg/500 mg/25 mg and Orphenadrine Forte (Orphen-
adrine Citrate, Aspirin and Caffeine 50 mg/770 mg/50 mg) Tablets are indicated in:

1. Symptomatic relief of mild to moderate pain of acute musculoskeletal disorders.

2. The orphenadrine compo-
nent is indicated as an ad-
junct to rest, physical thera-
py, and other measures for
the relief of discomfort as-
sociated with acute pain in
musculoskeletal conditions.

The mode of action of or-
phenadrine has not been clearly identified, but may be related to its analgesic prop-
eries. Orphenadrine Tablets and Orphenadrine Forte Tablets do not directly relax skeletal muscles in man.

CONTRAINDICATIONS

Because of the mild anticholin-
ergic effect of orphenadrine, Orphenadrine Tablets or Orphenadrine Forte Tablets...
should not be used in patients with glaucoma, prostate or dual
urinary obstruction, cardiovascular, hepatic, renal, or other multi-
organ involvement, or recently treated with radiation or chemother-
apy. "Ophthalmic Tablets or Ophthalmic Forte Tablets are also
contraindicated in patients with uncompensated heart disease
or patients known to be sensitive to aspirin or caffeine-containing
products.

The drug is contraindicated in patients who have dem-
strated a previous hypersensitiv-
ity to the drug.

MISCELLANEOUS

Reye's Syndrome may develop in individuals who have chicken
pox, influenza, or flu symptoms.

Some studies suggest a pos-
sible association between the de-
development of Reye's Syndrome and the use of medicines
containing aspirin or caffeine.

Ophthalmic Tablets (Dophenol, Ophthalmic Tablets, Ophthalmic Tablets, and Caffeine Tablets 25 mg/250
mg/750 mg and Ophthalmic Forte Tablets (Dopphol, Ophthalmic Tablets Tis, Asprex and Caffeine Tablets 50 mg/750 mg/40
mg/40 mg/40 mg/40 mg) are not recommended for use in patients with chicken pox, influenza, or flu symptoms.

Ophthalmic Tablets and Ophthalmic Forte Tablets may
mask the severity of the patient's illness or delay in the diagnosis of serious underlying conditions such as pres-
ence of a meningitis or encephalitis. Therefore, any patient who is acutely ill should receive appropriate antibacterial agents accordingly.

Aspirin should be used with es-
tensive caution in the presence of prostatic surgery and convulsion
anemia, arthritic joint, and cerebro-
vascular abnormalities.

Usage in Pregnancy:

Since safety of the use of this prepar-
ation in pregnant women during latio-

tation, or in children, the use of the drug in pregnant women is not
recommended.

Usage in Children:

The safety of this drug in children has not been estab-
lished. Usage of this drug in children under 12 years of age is not recommended.

PRECAUTIONS

Convulsions, anxiety, and fever have been reported in a few
patients receiving propy-
phrine and dopamine con-
comitantly. As these symptoms may be simply due to an additive
effect, reduction of dosage
dosage or discontinuation of one
or both agents is recommend-
ed in such cases.

Safety of continued long-term therapy with Ophthalmic Tablets and Ophthalmic Forte Tablets has not been estab-
lished. Therefore, Ophthalmic Tablets or Ophthalmic Forte Tablets are prescribed for pro-
tonigal use, pending evaluation of their
efficacy, tolerance, and overall safety.

ADVERSE REACTIONS

Side effects of Ophthalmic Tablets or Ophthalmic Forte Tablets are those seen with aspirin and caffeine or those usual-
ly associated with oral anti-
geranserig agents. These may
include tachycardia, palpitation, urinary hesitancy or retention, dry mouth, blurred vision, di-
tension of the pupil, increased intraocular tension, weakness, headache, swelling, and rarely, urticaria and other allergic reactions.
Side effects of Orrheosic Tablets or Orrheosic Forte Tablets are those seen with aspirin and caffeine or those usually associated with mild antihypertensive agents. These may include headache, palpitation, urinary frequency or retention, dry mouth, blurred vision, dilatation of the pupils, increased intracranial tension, restlessness, nausea, vomiting, tachycardia, dizziness, constipation, diarrhea, and nausea, urticaria and other dermatitis, intracranial hemorrhage, or oculogyria in elderly patients may experience some degree of confusion. Minor central excitation and occasional hallucinations may be observed. These mild side effects are usually alleviated 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 0.1 hemorrhage due to aspirin content may be associated with the administration of Orrheosic Tablets or Orrheosic Forte Tablets. Some patients may experience transient episodes of light-headedness, dizziness or syncope.

DOSAGE AND ADMINISTRATION

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

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

HOW SUPPLIED

Orrheosic Tablets (Orrheosic Forte Tablets)
325 mg and 10 mg (325 mg and 10 mg)
Two-layered white/green, round, unscored, flat-faced, bevelled-edge tablets debossed "3M" over "472" on the white side and "593" over "472" on the green side. Available in bottles of 100 tablets (NDC 49884-473-01) and 100 tablets (NDC 49884-472-00).

Orrheosic Forte Tablets
50 mg.
Aspirin 770 mg and caffeine 60 mg.
Two-layered, white/green capsule shaped tablets debossed "3M" and "472" with blister on the white side and plain on the green side. Available in bottles of 100 tablets (NDC 49884-473-01) and 100 tablets (NDC 49884-472-00).

Store below 30°C (86°F).

Manufactured by:
PAR PHARMACEUTICALS, 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)-. \( \text{C}_9\text{H}_8\text{O}_4 \). 180.16. 50-78-2. Analgesic, antipyretic, antirheumatic. USP 23, page 131.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{HO} & \quad \text{CO}
\end{align*}
\]

Caffeine. \( 1H \)-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl--.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} & \quad \text{CH}_3 \\
\text{O} & \quad \text{N} & \quad \text{N} & \quad \text{CH}_3 & \quad \text{O}
\end{align*}
\]

Orphenadrine Citrate. Ethanamine, \( N,N \)-dimethyl-2-[(2-methylphenyl)phenyl-methoxyl]-, \((\pm)\)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1). \( \text{C}_{18}\text{H}_{28}\text{NO}_5\text{C}_3\text{H}_4\text{O}_2 \). 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-Li Huang, Ph.D.  **DATE COMPLETED:** May 19, 1998

Endorsements:
- HFD-627/Liang-Li Huang, Ph.D. /5-19-98
- HFD-627/Paul Schwartz, Ph.D. /5-19-98
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

AMDA: #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 SITE:

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
SIGNATURE:  JF: 5/8/98
Acting Team Leader: M. Makary  BRANCH: III
SIGNATURE:  DATE: 5/8/98

DIRECTOR: Dale P. Conner
DIVISION OF BIOEQUIVALENCE:
SIGNATURE:  DATE: 5/11/98

DIRECTOR: Doug Sporn
OFFICE OF GENERIC DRUGS:
SIGNATURE:  DATE:
Aspirin/Caffeine/Orphenadrine Citrate
Par Pharmaceutical, Inc.
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

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 (DBB) 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 MMMAKARY
PT INITIALED MMMAKARY

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  X  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

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<th>Test Product: Lot #880086</th>
<th>Strength (mg)</th>
<th>Reference Product: Lot #931653</th>
<th>Strength (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 minutes</td>
<td>Mean = 77.2</td>
<td>Range = (7.1)</td>
<td>(CV%) = 75.0</td>
<td>Range = (4.4)</td>
</tr>
<tr>
<td>30 minutes</td>
<td>Mean = 92.8</td>
<td>Range = (2.8)</td>
<td>(CV%) = 95.7</td>
<td>Range = (3.9)</td>
</tr>
<tr>
<td>45 minutes</td>
<td>Mean = 96.2</td>
<td>Range = (2.4)</td>
<td>(CV%) = 96.2</td>
<td>Range = (3.1)</td>
</tr>
<tr>
<td>60 minutes</td>
<td>Mean = 96.4</td>
<td>Range = (1.9)</td>
<td>(CV%) = 94.1</td>
<td>Range = (2.9)</td>
</tr>
</tbody>
</table>

### C: Caffeine

<table>
<thead>
<tr>
<th>Sampling Times</th>
<th>Test Product: Lot #880086</th>
<th>Strength (mg)</th>
<th>Reference Product: Lot #931653</th>
<th>Strength (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 minutes</td>
<td>Mean = 30.4</td>
<td>Range = (33.0)</td>
<td>(CV%) = 70.1</td>
<td>Range = (29.4)</td>
</tr>
<tr>
<td>30 minutes</td>
<td>Mean = 30.4</td>
<td>Range = (25.8)</td>
<td>(CV%) = 81.5</td>
<td>Range = (16.7)</td>
</tr>
<tr>
<td>45 minutes</td>
<td>Mean = 27.0</td>
<td>Range = (2.1)</td>
<td>(CV%) = 98.3</td>
<td>Range = (10.1)</td>
</tr>
<tr>
<td>60 minutes</td>
<td>Mean = 28.8</td>
<td>Range = (1.9)</td>
<td>(CV%) = 91.5</td>
<td>Range = (5.3)</td>
</tr>
</tbody>
</table>
Table 2: In Vitro Dissolution Testing

Drug (Generic Name): Orphesic (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 X Paddle X RPM 50 No. Units Tested 12

Medium: water at 37° C Volume: 500 mL

Reference Drug: Norgesic Tablets

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

A: Orphenadrine Citrate

<table>
<thead>
<tr>
<th>Sampling Times</th>
<th>Test Product:</th>
<th>Reference Product:</th>
</tr>
</thead>
<tbody>
<tr>
<td>minutes</td>
<td>Lot #5B0078</td>
<td>Lot #930214</td>
</tr>
<tr>
<td></td>
<td>Strength (mg)</td>
<td>Strength (mg)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>58.1</td>
</tr>
<tr>
<td></td>
<td>22.1</td>
<td>(32.9) (12.1)</td>
</tr>
<tr>
<td></td>
<td>32.6</td>
<td>92.1</td>
</tr>
<tr>
<td></td>
<td>22.1</td>
<td>(12.1) (1.2)</td>
</tr>
<tr>
<td></td>
<td>100.5</td>
<td>97.5</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>(0.7) (7.6)</td>
</tr>
</tbody>
</table>


### B: Aspirin

<table>
<thead>
<tr>
<th>Sampling Times (minutes)</th>
<th>Test Product:</th>
<th>Reference Product:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lot #SB0078</td>
<td>Lot #930214</td>
</tr>
<tr>
<td></td>
<td>Strength (mg)</td>
<td>Strength (mg)</td>
</tr>
<tr>
<td></td>
<td>185</td>
<td>185</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
<th>(CV%)</th>
<th>Mean</th>
<th>Range</th>
<th>(CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>73.1</td>
<td>78.2</td>
<td>5.5</td>
<td>68.2</td>
<td>79.2</td>
<td>7.2</td>
</tr>
<tr>
<td>30</td>
<td>89.1</td>
<td>62.5</td>
<td>3.7</td>
<td>82.5</td>
<td>82.5</td>
<td>3.9</td>
</tr>
<tr>
<td>45</td>
<td>92.5</td>
<td>94.1</td>
<td>2.9</td>
<td>84.5</td>
<td>84.5</td>
<td>5.0</td>
</tr>
<tr>
<td>60</td>
<td>94.1</td>
<td>94.1</td>
<td>2.1</td>
<td>84.5</td>
<td>84.5</td>
<td>4.5</td>
</tr>
</tbody>
</table>

### C: Caffeine

<table>
<thead>
<tr>
<th>Sampling Times (minutes)</th>
<th>Test Product:</th>
<th>Reference Product:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lot #SB0078</td>
<td>Lot #930214</td>
</tr>
<tr>
<td></td>
<td>Strength (mg)</td>
<td>Strength (mg)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
<th>(CV%)</th>
<th>Mean</th>
<th>Range</th>
<th>(CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>50.2</td>
<td>33.6</td>
<td>32.7</td>
<td>25.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>91.9</td>
<td>12.8</td>
<td>81.2</td>
<td>16.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>92.0</td>
<td>2.7</td>
<td>90.0</td>
<td>11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>100.6</td>
<td>2.2</td>
<td>94.5</td>
<td>7.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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: June 09, 1997

I. Conditions for Dissolution Testing:

USP XXIII  Basket X  Paddle ___ RPM 75  No. Units Tested 12
Medium: water at 100°C  Volume: 900 mL
Reference Drug: Norcesic Forte Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

A: Orphenadrine Citrate

<table>
<thead>
<tr>
<th>Sampling Times (minutes)</th>
<th>Test Product: Strength (mg) 50</th>
<th>Reference Product: Strength (mg) 50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean %</td>
<td>Range % (CV%)</td>
</tr>
<tr>
<td>15</td>
<td>72.7</td>
<td>(12.4)</td>
</tr>
<tr>
<td>30</td>
<td>89.5</td>
<td>(0.9)</td>
</tr>
<tr>
<td>45</td>
<td>92.7</td>
<td>(1.0)</td>
</tr>
<tr>
<td>60</td>
<td>100.0</td>
<td>(1.0)</td>
</tr>
</tbody>
</table>
### B: Aspirin

<table>
<thead>
<tr>
<th>Sampling Times (minutes)</th>
<th>Test Product: Lot #SB0086</th>
<th>Reference Product: Lot #931653</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strength (mg) 770</td>
<td>Strength (mg) 770</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>15</td>
<td>47.7</td>
<td>72.1</td>
</tr>
<tr>
<td>30</td>
<td>86.3</td>
<td>92.3</td>
</tr>
<tr>
<td>45</td>
<td>24.2</td>
<td>27.8</td>
</tr>
<tr>
<td>60</td>
<td>25.4</td>
<td>28.2</td>
</tr>
</tbody>
</table>

### C: Caffeine

<table>
<thead>
<tr>
<th>Sampling Times (minutes)</th>
<th>Test Product: Lot #SB0086</th>
<th>Reference Product: Lot #931653</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strength (mg) 60</td>
<td>Strength (mg) 60</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>15</td>
<td>74.8</td>
<td>80.6</td>
</tr>
<tr>
<td>30</td>
<td>98.8</td>
<td>96.2</td>
</tr>
<tr>
<td>45</td>
<td>99.7</td>
<td>96.6</td>
</tr>
<tr>
<td>60</td>
<td>99.5</td>
<td>96.6</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Sampling Times</th>
<th>Test Product:</th>
<th>Reference Product:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lot #SB0078</td>
<td>Lot #930214</td>
</tr>
<tr>
<td>minutes</td>
<td>Strength (mg)</td>
<td>Strength (mg)</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range (CV)</th>
<th>Mean</th>
<th>Range (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>77.7</td>
<td>.5 (15.6)</td>
<td>74.5</td>
<td>(11.2)</td>
</tr>
<tr>
<td>30</td>
<td>27.2</td>
<td>0 (2.7)</td>
<td>101.0</td>
<td>(2.1)</td>
</tr>
<tr>
<td>45</td>
<td>58.9</td>
<td>1 (1.8)</td>
<td>101.1</td>
<td>(1.5)</td>
</tr>
<tr>
<td>60</td>
<td>29.0</td>
<td>2 (2.1)</td>
<td>101.5</td>
<td>(1.5)</td>
</tr>
</tbody>
</table>
### B: Aspirin

<table>
<thead>
<tr>
<th>Sampling Times (minutes)</th>
<th>Test Product: Lot #SB0078</th>
<th>Reference Product: Lot #930214</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strength (mg) 385</td>
<td>Strength (mg) 385</td>
</tr>
<tr>
<td>Mean</td>
<td>Range (CV%)</td>
<td>Mean</td>
</tr>
<tr>
<td>15</td>
<td>80.0 (8.9)</td>
<td>76.1</td>
</tr>
<tr>
<td>30</td>
<td>95.5 (1.7)</td>
<td>99.2</td>
</tr>
<tr>
<td>45</td>
<td>96.5 (0.9)</td>
<td>91.3</td>
</tr>
<tr>
<td>60</td>
<td>95.5 (1.5)</td>
<td>91.3</td>
</tr>
</tbody>
</table>

### C: Caffeine

<table>
<thead>
<tr>
<th>Sampling Times (minutes)</th>
<th>Test Product: Lot #SB0078</th>
<th>Reference Product: Lot #930214</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strength (mg) 385</td>
<td>Strength (mg) 385</td>
</tr>
<tr>
<td>Mean</td>
<td>Range (CV%)</td>
<td>Mean</td>
</tr>
<tr>
<td>15</td>
<td>79.8 (12.2)</td>
<td>75.2</td>
</tr>
<tr>
<td>30</td>
<td>99.0 (3.1)</td>
<td>101.7</td>
</tr>
<tr>
<td>45</td>
<td>99.5 (2.2)</td>
<td>101.2</td>
</tr>
<tr>
<td>60</td>
<td>99.9 (2.7)</td>
<td>101.5</td>
</tr>
</tbody>
</table>
Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 22-Mar-1998 10:51pm EST
From: John Lazor
LAZOR
Dept: HFD-880 CRP2 N108
Tel No: 301-827-2005 FAX 301-827-2575

To: Nhan Tran

Subject: Norgesic Forte

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

In a 1993 letter to the company, their proposal was accepted. A review by Dennis Bashaw in 1993 indicated that the Q was 75%, however he indicates that was in error. He accepted the company's proposal of 70%.

We will be writing a memo to the NDA to clarify this.

The method and specification are:

Apparatus I (Basket)
2 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 bioequivalence 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
HFD-650/ D. Conner 5/8/98

BIOEQUIVALENCY - ACCEPTABLE

/5/30-97 1. DISSOLUTION DATA (DIS)

All Strengths: 50mg/770mg/60mg
25mg/385mg/30mg
Outcome: AC

/3/4-98 2. STUDY AMENDMENT (STA)

Strength: 50mg/770mg/60mg
Outcome: AC

/2/21-98 3. STA

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, 5/6/98).

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
ANDA APPROVAL SUMMARY: 75-141

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

The tablets of the exhibit batch of the Orphengesic Tablets (Orphendraine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg) (lot#SB0078) and the tablets of the Orphengesic Forte Tablets (Orphendraine 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-Liu Huang, Ph.D.).

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

(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 (Orphendraine citrate 25 mg, Aspirin 385 mg and Caffeine 30 mg) and tablets for the Orphengesic Forte Tablets (Orphendraine 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-Liu Huang, Ph.D. DATE: May 19, 1998
SUPERVISOR: Paul Schwartz, Ph.D. DATE: May 19, 1998
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
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.

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
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
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
Orphenegics Tablets
(Orphenadrine Citrate, Aspirin and Caffeine Tablets 25 mg/385 mg/30 mg
Orphenegics 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 Orphenegics and Orphenegics 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 I (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
Associate Director, Regulatory Affairs/R&D

RECEIVED
MAY 18 1993

GENERIC DRUGS
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

RE: ANDA 75-141
ORPHEGENSIC TABLETS
(Orphenadrine Citrate, Aspirin and Caffeine Tablets 25 mg/385 mg/30 mg)

ORPHEGENSIC 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 ORP-75 should be Orphengenic Forte Tablets.
ANDA 75-141
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)

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 inserts 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.

[Signature]

Teresa Tung
Senior Regulatory Affairs Associate

Enclosed

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