CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 90-619

Name: Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Sponsor: Dr. Reddy's Laboratories, Inc.

Approval Date: July 8, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-619

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-619

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-619

Dr. Reddy's Laboratories, Inc.
U.S. Agent for Dr. Reddy's Laboratories Limited
Attention: Kumara Sekar, Ph.D.
Sr. Director, Global Regulatory Affairs
200 Somerset Corporate Blvd., Building II, 7th Floor
Bridgewater, NJ 08807

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated June 13, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg.

Reference is also made to your amendments dated December 12, December 26, and December 30, 2008; and January 29, February 26, April 10, and April 17, 2009.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for over-the-counter (OTC) use as recommended in the submitted labeling. Accordingly, the ANDA is approved effective on the date of this letter. The Division of Bioequivalence has determined your Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg, to be therapeutically equivalent to the reference listed drug, Advil PM Caplets, 200 mg/38 mg, of Wyeth Consumer Healthcare. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA 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.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert L. West
7/8/2009 12:12:40 PM
Deputy Director, for Gary Buehler

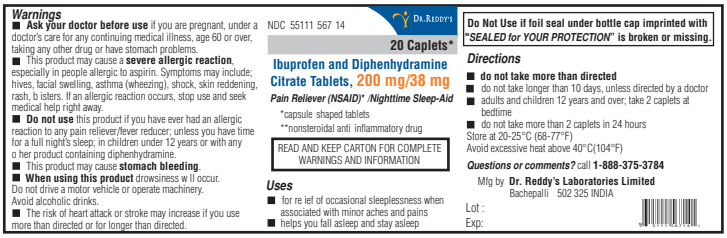
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-619

LABELING

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 20's count
Actual Label Size: 95 mm x 30 mm



Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, b isters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any o her product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness w ll occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

NDC 55111 567 14

Dr. Reddy's

20 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)* /Nighttime Sleep-Aid

*capsule shaped tablets

**nonsteroidal anti inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for re ief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with "*SEALED for YOUR PROTECTION*" is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

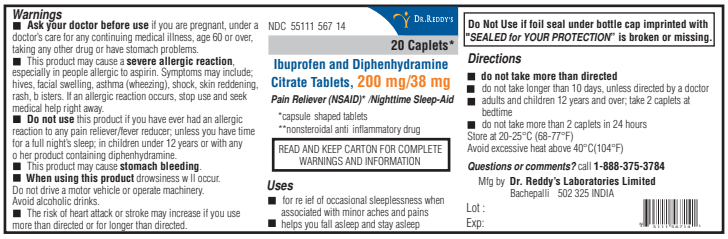
Mfg by **Dr. Reddy's Laboratories Limited**
Bachepalli 502 325 INDIA

Lot :

Exp:

(b) (4)

(b) (4)



Warnings

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■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness w ll occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

NDC 55111 567 14

Dr. Reddy's

20 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)* /Nighttime Sleep-Aid

*capsule shaped tablets

**nonsteroidal anti inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

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■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with "*SEALED for YOUR PROTECTION*" is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

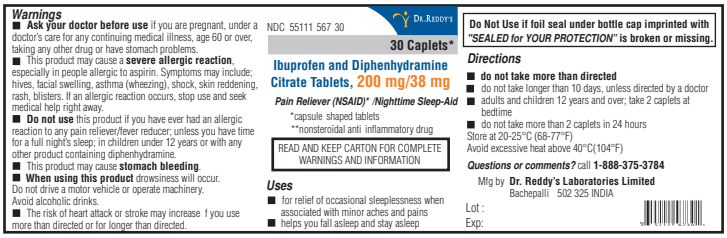
Questions or comments? call **1-888-375-3784**

Mfg by **Dr. Reddy's Laboratories Limited**
Bachepalli 502 325 INDIA

Lot :

Exp:

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 30's count
Actual Label Size: 95 mm x 30 mm



Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur.
Do not drive a motor vehicle or operate machinery.
Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase f you use more than directed or for longer than directed.

NDC 55111 567 30

Dr. Reddy's

30 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)* /Nighttime Sleep-Aid

*capsule shaped tablets
**nonsteroidal anti inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor
■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours
Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)

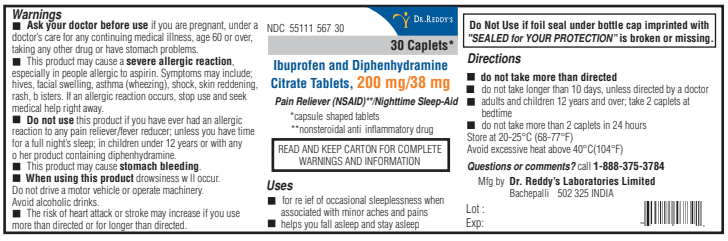
Questions or comments? call **1-888-375-3784**

Mfg by **Dr. Reddy's Laboratories Limited**
Bachepalli 502 325 INDIA

Lot :
Exp:

(b) (4)

(b) (4)



Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, b isters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any o her product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness w ll occur.
Do not drive a motor vehicle or operate machinery.
Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

NDC 55111 567 30

Dr. Reddy's

30 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule shaped tablets
**nonsteroidal anti inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for re ief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

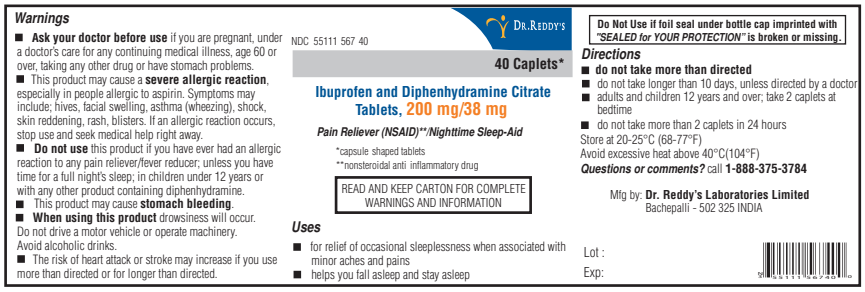
■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor
■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours
Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

Mfg by **Dr. Reddy's Laboratories Limited**
Bachepalli 502 325 INDIA

Lot :
Exp:

Final Container Label
Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg - 40's count
Actual Label Size: 113 mm x 37 mm



Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.
■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.
■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.
■ This product may cause **stomach bleeding**.
■ **When using this product** drowsiness will occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.
■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

DR. REDDY'S

NDC 55111 567 40

40 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule shaped tablets
**nonsteroidal anti inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor
■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours

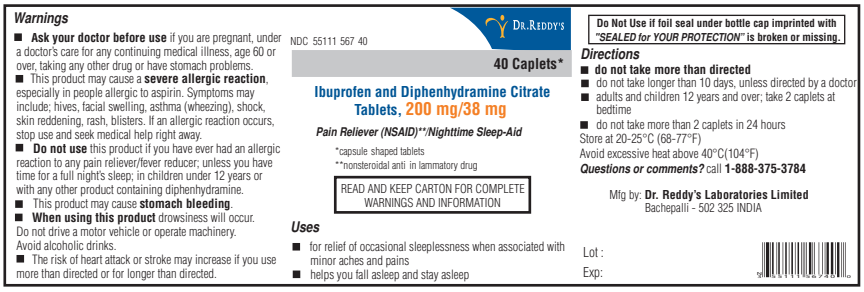
Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)
Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :
Exp:

(b) (4)

(b) (4)



Warnings

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DR. REDDY'S

NDC 55111 567 40

40 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule shaped tablets
**nonsteroidal anti in lammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor
■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)
Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :
Exp:

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 80's count
Actual Label Size: 120 mm x 40 mm

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.
■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.
■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.
■ This product may cause **stomach bleeding**.
■ **When using this product** drowsiness will occur.
Do not drive a motor vehicle or operate machinery.
Avoid alcoholic drinks.
■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

DR. REDDY'S

NDC 55111-567-80

80 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets
**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor
■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours
Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)
Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :
Exp:

(b) (4)

(b) (4)

Warnings

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■ This product may cause **stomach bleeding**.
■ **When using this product** drowsiness will occur.
Do not drive a motor vehicle or operate machinery.
Avoid alcoholic drinks.
■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

DR. REDDY'S

NDC 55111-567-80

80 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets
**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

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Directions

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■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours
Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)
Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :
Exp:

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 90's count
Actual Label Size: 135 mm x 50 mm

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

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■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

Dr. Reddy's

NDC 55111-567-90

90 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

(b) (4)

(b) (4)

Warnings

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■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

Dr. Reddy's

NDC 55111-567-90

90 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 180's count
Actual Label Size: 145 mm x 60 mm

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

NDC 55111-567-18

DR.REDDY'S

180 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

3 55111 56718 9

(b) (4)

(b) (4)

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

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■ This product may cause **stomach bleeding**.

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■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

NDC 55111-567-18

DR.REDDY'S

180 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

3 55111 56718 9

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 500's count
Actual Label Size: 170 mm x 90 mm

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur.

Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

DR.REDDY'S

NDC 55111-567-05

500 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments?

call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

(b) (4)

(b) (4)

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur.

Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

DR.REDDY'S

NDC 55111-567-05

500 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments?

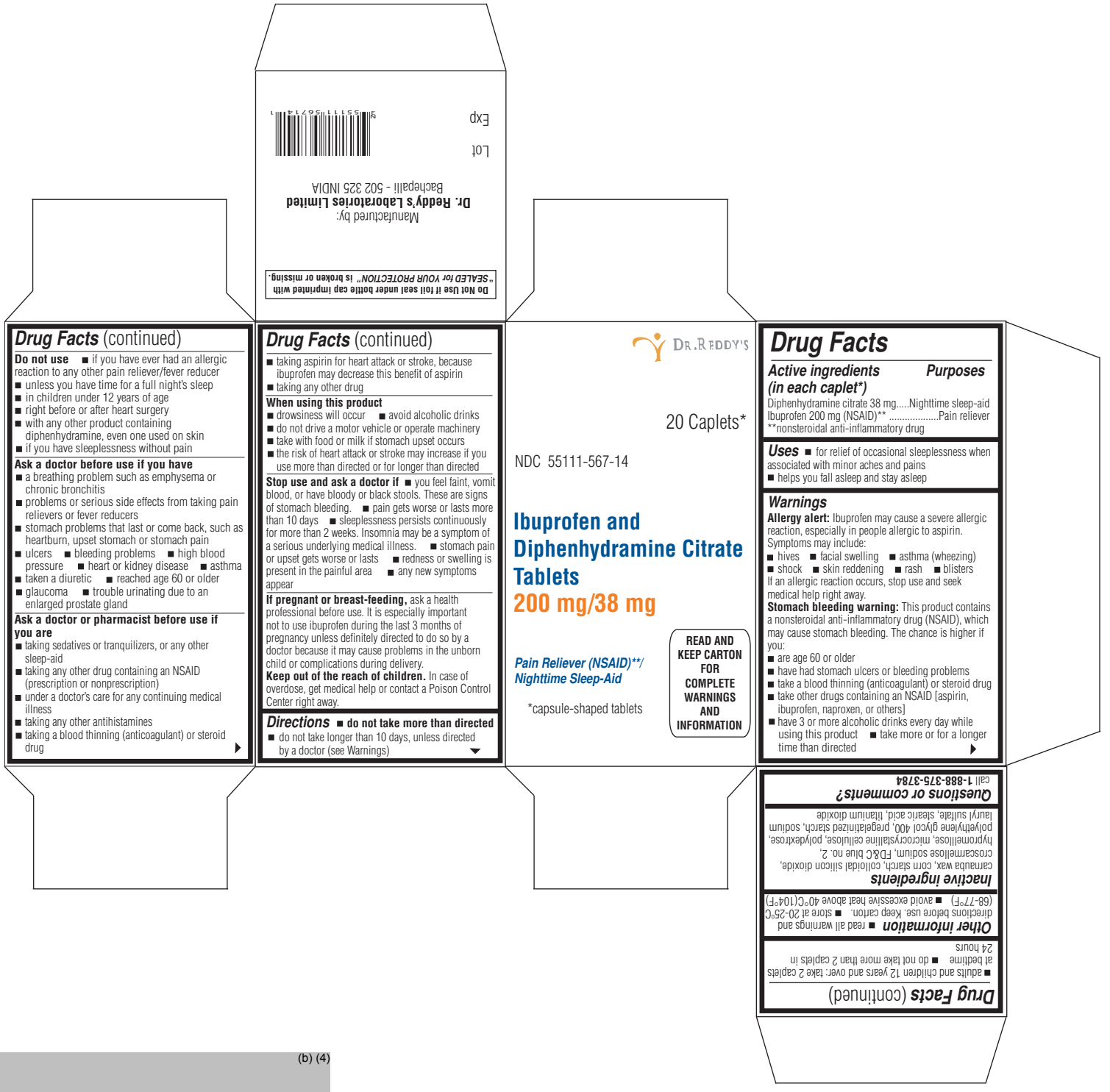
call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 20's count
Actual Label Size: 45 mm x 45 mm x 80 mm



Exp

Lot

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

Do Not Use if foil seal under bottle cap imprinted with "*SEALED for YOUR PROTECTION*" is broken or missing.

Drug Facts (continued)

Do not use ■ if you have ever had an allergic reaction to any other pain reliever/fever reducer
■ unless you have time for a full night's sleep
■ in children under 12 years of age
■ right before or after heart surgery
■ with any other product containing diphenhydramine, even one used on skin
■ if you have sleeplessness without pain

Ask a doctor before use if you have
■ a breathing problem such as emphysema or chronic bronchitis
■ problems or serious side effects from taking pain relievers or fever reducers
■ stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
■ ulcers ■ bleeding problems ■ high blood pressure ■ heart or kidney disease ■ asthma
■ taken a diuretic ■ reached age 60 or older
■ glaucoma ■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are
■ taking sedatives or tranquilizers, or any other sleep-aid
■ taking any other drug containing an NSAID (prescription or nonprescription)
■ under a doctor's care for any continuing medical illness
■ taking any other antihistamines
■ taking a blood thinning (anticoagulant) or steroid drug ▶

Drug Facts (continued)

■ taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
■ taking any other drug

When using this product
■ drowsiness will occur ■ avoid alcoholic drinks
■ do not drive a motor vehicle or operate machinery
■ take with food or milk if stomach upset occurs
■ the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

Stop use and ask a doctor if ■ you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. ■ pain gets worse or lasts more than 10 days ■ sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness. ■ stomach pain or upset gets worse or lasts ■ redness or swelling is present in the painful area ■ any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor (see Warnings) ▼

DR. REDDY'S

20 Caplets*

NDC 55111-567-14

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

Pain Reliever (NSAID)**/ Nighttime Sleep-Aid

*capsule-shaped tablets

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Drug Facts

Active ingredients (in each caplet*)	***Purposes***
Diphenhydramine citrate 38 mg	Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)**	Pain reliever

**nonsteroidal anti-inflammatory drug

Uses ■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
■ hives ■ facial swelling ■ asthma (wheezing)
■ shock ■ skin reddening ■ rash ■ blisters
If an allergic reaction occurs, stop use and seek medical help right away.
Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:
■ are age 60 or older
■ have had stomach ulcers or bleeding problems
■ take a blood thinning (anticoagulant) or steroid drug
■ take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
■ have 3 or more alcoholic drinks every day while using this product ■ take more or for a longer time than directed ▶

Questions or comments?
call **1-888-375-3784**

Inactive ingredients
carnauba wax, corn starch, colloidal silicon dioxide, croscarmellose sodium, FD&C blue no. 2, hypromellose, microcrystalline cellulose, polydextrose, polyethylene glycol 400, pregelatinized starch, sodium lauryl sulfate, stearic acid, titanium dioxide

Other information ■ read all warnings and directions before use. Keep carton. ■ store at 20-25°C (68-77°F) ■ avoid excessive heat above 40°C(104°F)

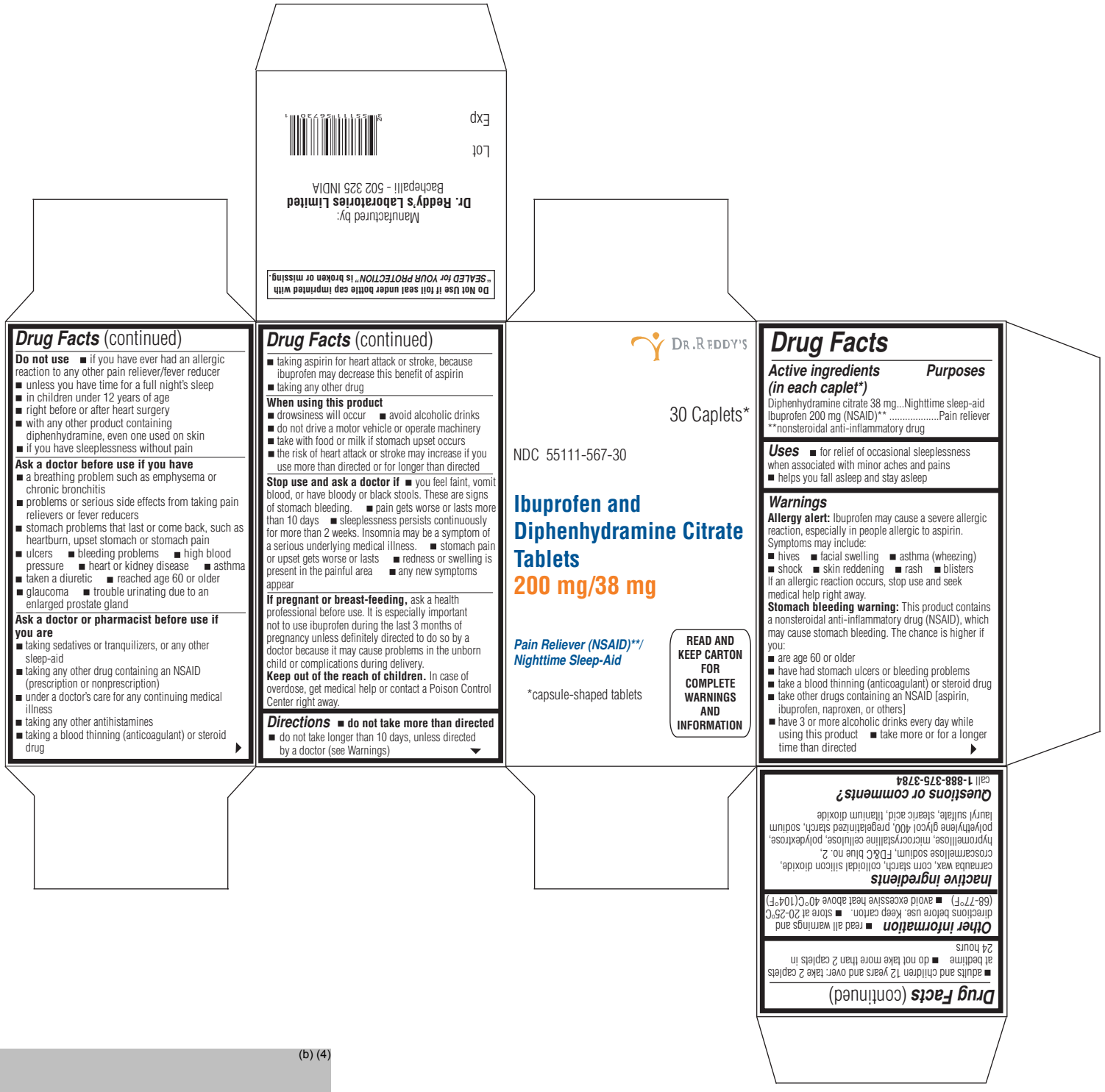
Drug Facts (continued)

■ adults and children 12 years and over: take 2 caplets at bedtime ■ do not take more than 2 caplets in 24 hours

(b) (4)

(b) (4)

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 30's count
Actual Label Size: 45 mm x 45 mm x 80 mm



Exp

Lot

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

Do Not Use if foil seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

Drug Facts (continued)

Do not use ■ if you have ever had an allergic reaction to any other pain reliever/fever reducer
■ unless you have time for a full night's sleep
■ in children under 12 years of age
■ right before or after heart surgery
■ with any other product containing diphenhydramine, even one used on skin
■ if you have sleeplessness without pain

Ask a doctor before use if you have
■ a breathing problem such as emphysema or chronic bronchitis
■ problems or serious side effects from taking pain relievers or fever reducers
■ stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
■ ulcers ■ bleeding problems ■ high blood pressure ■ heart or kidney disease ■ asthma
■ taken a diuretic ■ reached age 60 or older
■ glaucoma ■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are
■ taking sedatives or tranquilizers, or any other sleep-aid
■ taking any other drug containing an NSAID (prescription or nonprescription)
■ under a doctor's care for any continuing medical illness
■ taking any other antihistamines
■ taking a blood thinning (anticoagulant) or steroid drug

Drug Facts (continued)

■ taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
■ taking any other drug

When using this product
■ drowsiness will occur ■ avoid alcoholic drinks
■ do not drive a motor vehicle or operate machinery
■ take with food or milk if stomach upset occurs
■ the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

Stop use and ask a doctor if ■ you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. ■ pain gets worse or lasts more than 10 days ■ sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness. ■ stomach pain or upset gets worse or lasts ■ redness or swelling is present in the painful area ■ any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor (see Warnings)

DR. REDDY'S

30 Caplets*

NDC 55111-567-30

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

*Pain Reliever (NSAID)**/ Nighttime Sleep-Aid*

*capsule-shaped tablets

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Drug Facts

Active ingredients (in each caplet*)	Purposes
Diphenhydramine citrate 38 mg	Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)**	Pain reliever

**nonsteroidal anti-inflammatory drug

Uses ■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
■ hives ■ facial swelling ■ asthma (wheezing)
■ shock ■ skin reddening ■ rash ■ blisters
If an allergic reaction occurs, stop use and seek medical help right away.
Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:
■ are age 60 or older
■ have had stomach ulcers or bleeding problems
■ take a blood thinning (anticoagulant) or steroid drug
■ take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
■ have 3 or more alcoholic drinks every day while using this product ■ take more or for a longer time than directed

Drug Facts (continued)

■ adults and children 12 years and over: take 2 caplets at bedtime ■ do not take more than 2 caplets in 24 hours

Other information ■ read all warnings and directions before use. Keep carton. ■ store at 20-25°C (68-77°F) ■ avoid excessive heat above 40°C(104°F)

Inactive ingredients
carnauba wax, corn starch, colloidal silicon dioxide, croscarmellose sodium, FD&C blue no. 2, hypromellose, microcrystalline cellulose, polydextrose, polyethylene glycol 400, pregelatinized starch, sodium lauryl sulfate, stearic acid, titanium dioxide

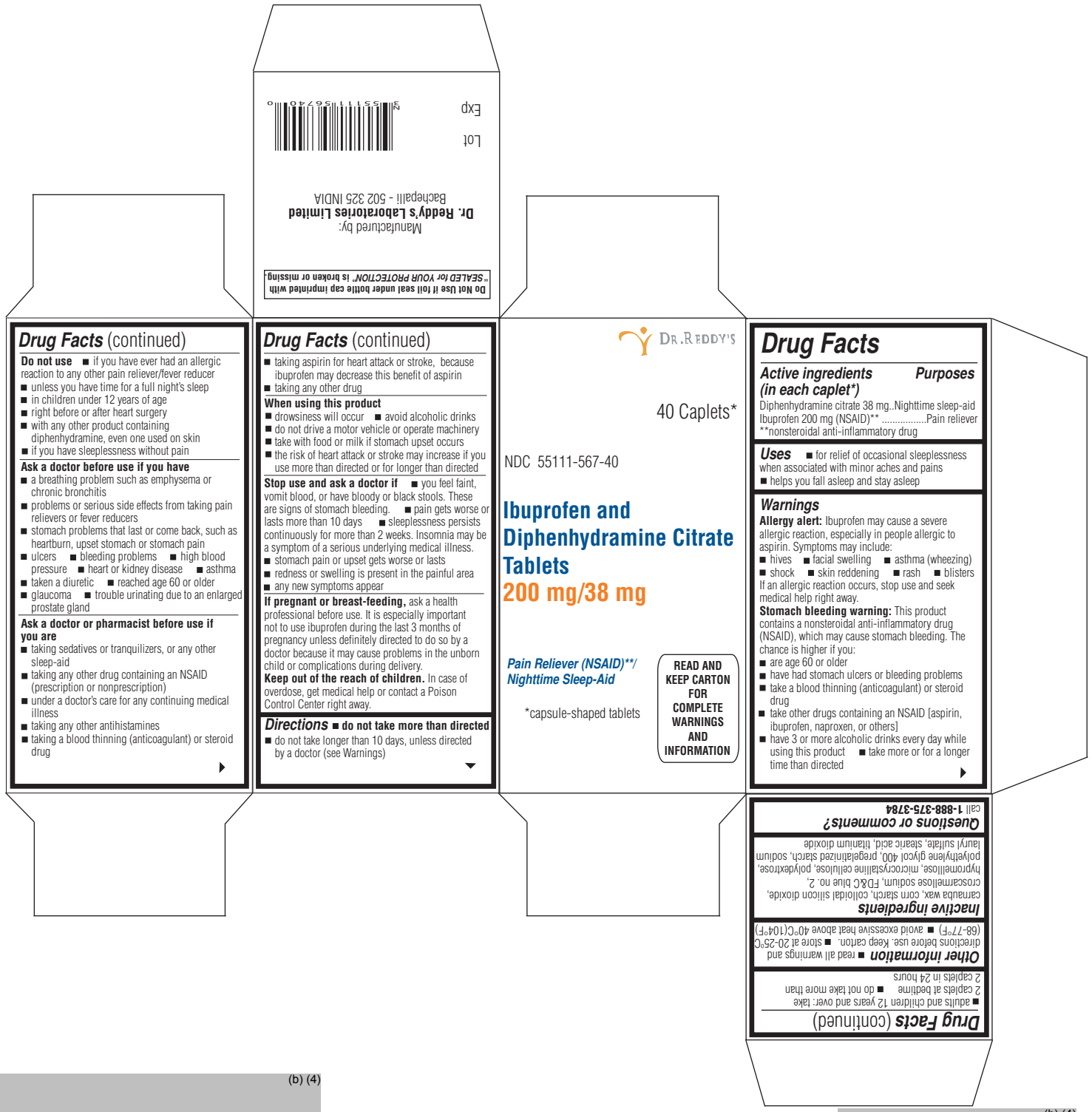
Questions or comments?
call **1-888-375-3784**

(b) (4)

(b) (4)

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 40's count

Actual Label Size: 44 mm x 44 mm x 85 mm



Lot

Exp

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

Do Not Use if foil seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

Drug Facts (continued)

Do not use ■ if you have ever had an allergic reaction to any other pain reliever/fever reducer
■ unless you have time for a full night's sleep
■ in children under 12 years of age
■ right before or after heart surgery
■ with any other product containing diphenhydramine, even one used on skin
■ if you have sleeplessness without pain

Ask a doctor before use if you have
■ a breathing problem such as emphysema or chronic bronchitis
■ problems or serious side effects from taking pain relievers or fever reducers
■ stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
■ ulcers ■ bleeding problems ■ high blood pressure ■ heart or kidney disease ■ asthma
■ taken a diuretic ■ reached age 60 or older
■ glaucoma ■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are
■ taking sedatives or tranquilizers, or any other sleep-aid
■ taking any other drug containing an NSAID (prescription or nonprescription)
■ under a doctor's care for any continuing medical illness
■ taking any other antihistamines
■ taking a blood thinning (anticoagulant) or steroid drug

Drug Facts (continued)

■ taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
■ taking any other drug

When using this product
■ drowsiness will occur ■ avoid alcoholic drinks
■ do not drive a motor vehicle or operate machinery
■ take with food or milk if stomach upset occurs
■ the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

Stop use and ask a doctor if ■ you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. ■ pain gets worse or lasts more than 10 days ■ sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness.
■ stomach pain or upset gets worse or lasts
■ redness or swelling is present in the painful area
■ any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ do not take more than directed

■ do not take longer than 10 days, unless directed by a doctor (see Warnings)

DR. REDDY'S

40 Caplets*

NDC 55111-567-40

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

*Pain Reliever (NSAID)**/
Nighttime Sleep-Aid

*capsule-shaped tablets

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Drug Facts

Active ingredients (in each caplet*) ***Purposes***
Diphenhydramine citrate 38 mg..Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)** .....Pain reliever
**nonsteroidal anti-inflammatory drug

Uses ■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
■ hives ■ facial swelling ■ asthma (wheezing)
■ shock ■ skin reddening ■ rash ■ blisters
If an allergic reaction occurs, stop use and seek medical help right away.
Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:
■ are age 60 or older
■ have had stomach ulcers or bleeding problems
■ take a blood thinning (anticoagulant) or steroid drug
■ take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
■ have 3 or more alcoholic drinks every day while using this product ■ take more or for a longer time than directed

Drug Facts (continued)

Do not use ■ adults and children 12 years and over: take 2 caplets at bedtime ■ do not take more than 2 caplets in 24 hours

Other information ■ read all warnings and directions before use. Keep carton. ■ store at 20-25°C (68-77°F) ■ avoid excessive heat above 40°C(104°F)

Inactive ingredients
carnauba wax, corn starch, colloidal silicon dioxide, croscarmellose sodium, FD&C blue no. 2, hypromellose, microcrystalline cellulose, polydextrose, polyethylene glycol 400, pregelatinized starch, sodium lauryl sulfate, stearic acid, titanium dioxide

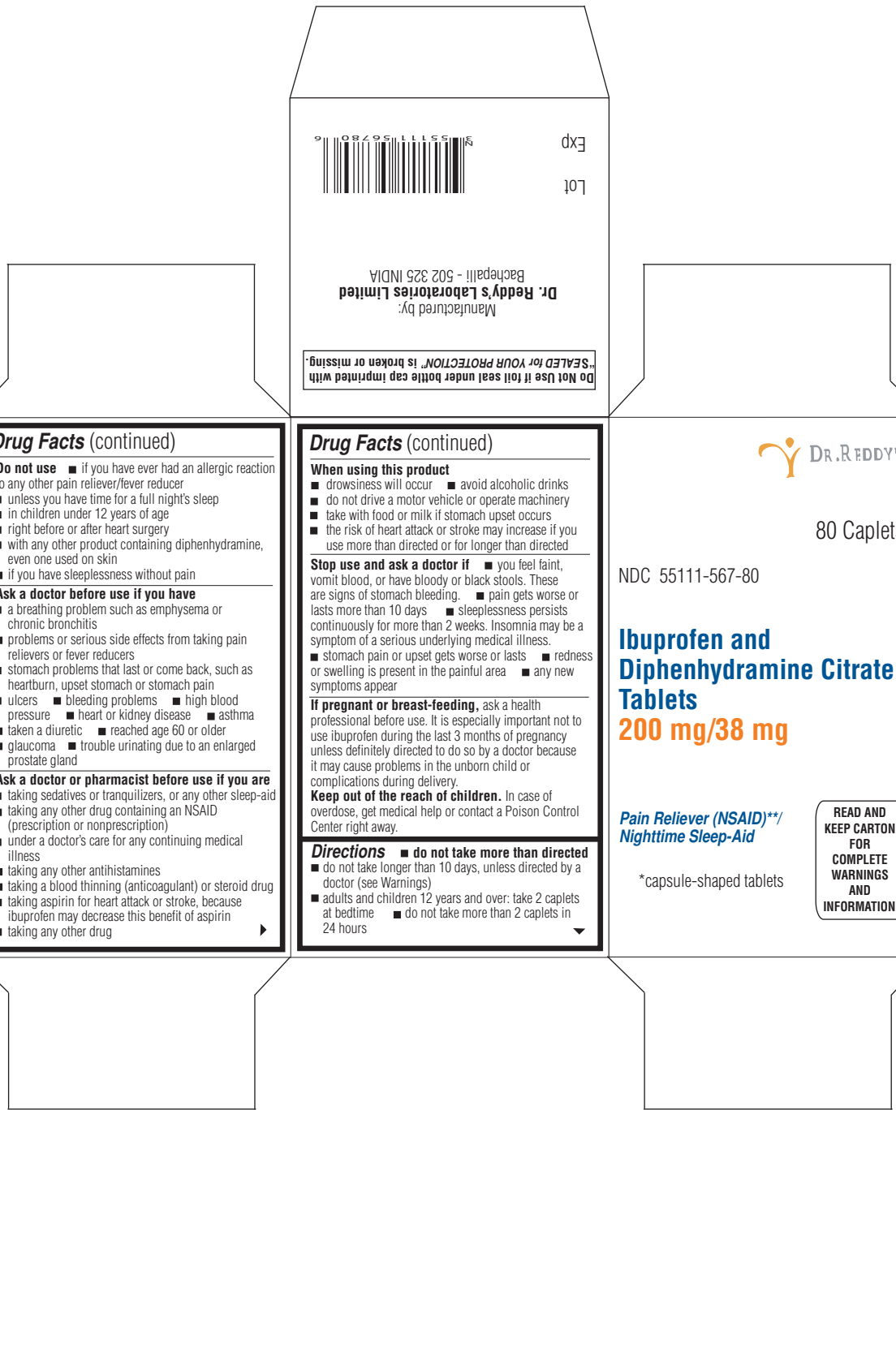
Questions or comments?
call **1-888-375-3784**

(b) (4)

(b) (4)

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 80's count

Actual Label Size: 52 mm x 52 mm x 88 mm

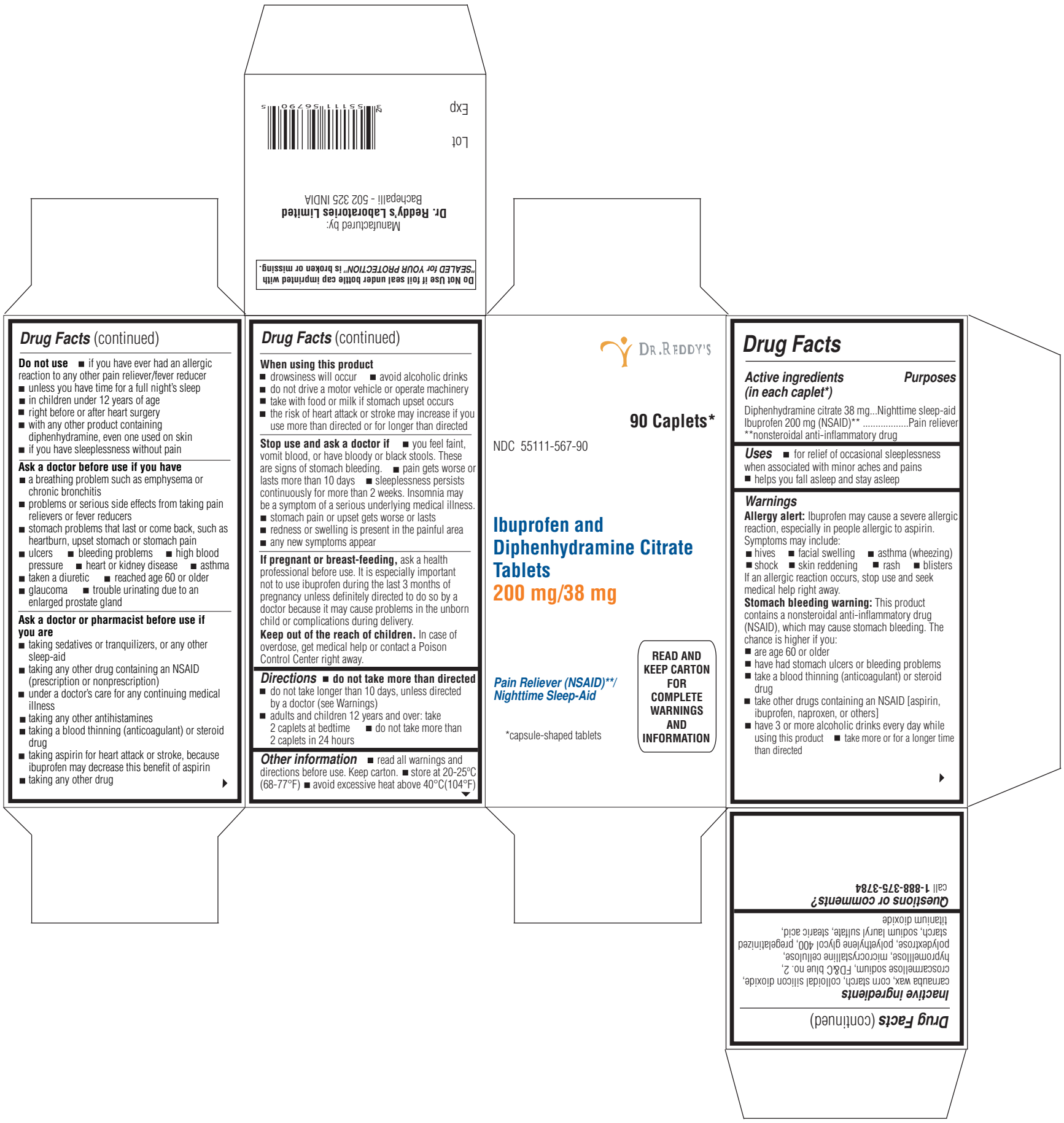


(b) (4)

(b) (4)

NOTE: This Container Carton is fit to paper print

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 90's count
Actual Label Size: 52 mm x 52 mm x 106 mm



(b) (4)

(b) (4)

NOTE: This Container Carton is fit to paper print

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 180's count

Actual Label Size: 60 mm x 60 mm x 126 mm

Lot

Exp

Do Not Use if foil seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

Drug Facts (continued)

- with any other product containing diphenhydramine, even one used on skin
- if you have sleeplessness without pain

Ask a doctor before use if you have

- a breathing problem such as emphysema or chronic bronchitis
- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
- ulcers ■ bleeding problems ■ high blood pressure ■ heart or kidney disease ■ asthma
- taken a diuretic ■ reached age 60 or older
- glaucoma ■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are

- taking sedatives or tranquilizers, or any other sleep-aid
- taking any other drug containing an NSAID (prescription or nonprescription)
- under a doctor's care for any continuing medical illness
- taking any other antihistamines
- taking a blood thinning (anticoagulant) or steroid drug
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product

- drowsiness will occur ■ avoid alcoholic drinks
- do not drive a motor vehicle or operate machinery
- take with food or milk if stomach upset occurs
- the risk of heart attack or storke may increase if you use more than directed or for longer than directed

Drug Facts (continued)

Stop use and ask a doctor if ■ you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. ■ pain gets worse or lasts more than 10 days ■ sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness.
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions **■ do not take more than directed**
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 2 caplets at bedtime ■ do not take more than 2 caplets in 24 hours

Other information ■ read all warnings and directions before use. Keep carton. ■ store at 20-25°C (68-77°F) ■ avoid excessive heat above 40°C(104°F)

Inactive ingredients
carnauba wax, corn starch, colloidal silicon dioxide, croscarmellose sodium, FD&C blue no. 2, hypromelllose, microcrystalline cellulose, polydextrose, polyethylene glycol 400, pregelatinized starch, sodium lauryl sulfate, stearic acid, titanium dioxide

Questions or comments?
call **1-888-375-3784**

DR. REDDY'S

180 Caplets*

NDC 55111-567-18

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

Pain Reliever (NSAID)**/ Nighttime Sleep-Aid

*capsule-shaped tablets

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Drug Facts

Active ingredients (in each caplet*) ***Purposes***
Diphenhydramine citrate 38 mg...Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)** .....Pain reliever
**nonsteroidal anti-inflammatory drug

Uses ■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
- hives ■ facial swelling ■ asthma (wheezing)
- shock ■ skin reddening ■ rash ■ blisters

If an allergic reaction occurs, stop use and seek medical help right away.
Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:
- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product ■ take more or for a longer time than directed

Do not use ■ if you have ever had an allergic reaction to any other pain reliever/fever reducer
- unless you have time for a full night's sleep
- in children under 12 years of age
- right before or after heart surgery

(b) (4)

(b) (4)

NOTE: This Container Carton is fit to paper print

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 500's count
Actual Label Size: 82 mm x 82 mm x 160 mm

Lot

Exp

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

Do Not Use if foil seal under bottle cap imprinted with "*SEALED for YOUR PROTECTION*" is broken or missing.

Drug Facts (continued)

Ask a doctor before use if you have
- a breathing problem such as emphysema or chronic bronchitis
- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
- ulcers ■ bleeding problems ■ high blood pressure ■ heart or kidney disease ■ asthma
- taken a diuretic ■ reached age 60 or older
- glaucoma ■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are
- taking sedatives or tranquilizers, or any other sleep-aid
- taking any other drug containing an NSAID (prescription or nonprescription)
- under a doctor's care for any continuing medical illness
- taking any other antihistamines
- taking a blood thinning (anticoagulant) or steroid drug
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product
- drowsiness will occur ■ avoid alcoholic drinks
- do not drive a motor vehicle or operate machinery
- take with food or milk if stomach upset occurs
- the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

Stop use and ask a doctor if ■ you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. ■ pain gets worse or lasts more than 10 days ■ sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness.

Drug Facts (continued)

- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ do not take more than directed
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 2 caplets at bedtime ■ do not take more than 2 caplets in 24 hours

Other information ■ read all warnings and directions before use. Keep carton. ■ store at 20-25°C (68-77°F) ■ avoid excessive heat above 40°C(104°F)

Inactive ingredients
carnauba wax, corn starch, colloidal silicon dioxide, croscarmellose sodium, FD&C blue no. 2, hypromelllose, microcrystalline cellulose, polydextrose, polyethylene glycol 400, pregelatinized starch, sodium lauryl sulfate, stearic acid, titanium dioxide

Questions or comments?
call **1-888-375-3784**

DR. REDDY'S

500 Caplets*

NDC 55111-567-05

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

Pain Reliever (NSAID)**/
Nighttime Sleep-Aid

*capsule-shaped tablets

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Drug Facts

Active ingredients (in each caplet*) — ***Purposes***
Diphenhydramine citrate 38 mg.....Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)** .....Pain reliever
**nonsteroidal anti-inflammatory drug

Uses
■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
■ hives ■ facial swelling ■ asthma (wheezing)
■ shock ■ skin reddening ■ rash ■ blisters
If an allergic reaction occurs, stop use and seek medical help right away.
Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:
- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product ■ take more or for a longer time than directed

Do not use ■ if you have ever had an allergic reaction to any other pain reliever/fever reducer
- unless you have time for a full night's sleep
- in children under 12 years of age
- right before or after heart surgery
- with any other product containing diphenhydramine, even one used on skin
- if you have sleeplessness without pain

(b) (4)

(b) (4)

NOTE: This Container Carton is fit to paper print

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-619

LABELING REVIEWS

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	90-619
Date of Submission:	April 10, 2009
Applicant's Name:	Dr. Reddys Laboratories
Established Name:	Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

---

Approval Summary:

1. **Do you have copies of final printed labels and labeling?** Yes

2. **CONTAINER – Bottles 20s, 30s, 40s, 80s, 90s, 180s and 500s**
   Satisfactory in **final print** as of the April 10, 2009 electronic submission

3. **CARTONS - 20s, 30s, 40s, 80s, 90s, 180s and 500s**
   Satisfactory in **final print** as of the April 10, 2009 electronic submission

4. **Revisions needed post-approval:** No

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Advil PM®
NDA Number: N 21-394
NDA Drug Name: Advil PM®
NDA Firm: Wyeth Consumer Healthcare
Date of Approval of NDA Insert and supplement: (NDA N 21-394/S-012); approved May 19, 2009
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Advil PM®
Other Comments: None

FOR THE RECORD:

1. Professional Package Insert:
   Model labeling used by the firm for Advil PM® was approved May 19, 2009; (N 21-394/S-012).

2. Storage/Dispensing Conditions:
   NDA: Store at 20º-25ºC(68º-77ºF). Avoid excessive heat above 40°C (104°F).
   ANDA: Store at 20-25°C (68-77°F). Avoid excessive heat above 40°C (104°F).

3. Product Line:
   RLD – 4, 20, 40 and 80 count container/carton
   ANDA – 20, 30, 40, 80, 90, 180 and 500 count bottles

4. Inactive Ingredients:
   The listing of the inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition statement.

Description and Composition of the Drug Product

What are the components and composition of the final product? What is the function(s) of each excipient? See the following tables. **Satisfactory**

			Inactive Ingredient Database		
S. No.	**Component**	**mg per tablet**	**Maximum Potency**	**Route of Administratio**	**Pharmaceutical Function**
[redacted] (b) (4)					

5. Container/Closure: The proposed container/closure system is a [redacted] (b) (4) bottle with a [redacted] (b) (4) cap and is commonly used for solid oral dosage forms. The proposed container/closure system has been qualified as safe for use with this dosage form.

Ibuprofen and Diphenhydramine citrate caplets 200/38 mg:

Container Packaging:

Package Size	Configuration
20's	• (b) (4) •  • • Container label
30's	• (b) (4) •  • • Container label
40's	• (b) (4) •  • • Container label
80's	• (b) (4) •  • • Container label
90's	• (b) (4) •  • • Container label
180's	• (b) (4) •  • • Container label
500's	• (b) (4) •  • • Container label

6. All manufacturing will be performed by:

Dr. Reddy's Laboratories Limited (Generics)
Located at Bachepalli – 502 325
INDIA

7. Patent Information

Patent Data – NDA 21-394

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	*None*	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 21-394

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	*N/A*	*None*

8. Tablet Imprintings:
   Blue colored, capsule shaped, biconvex, film coated tablets debossed 'RDY' on one side and '565' on the other side.

9. The minimum font size required in the labeling has been utilized.

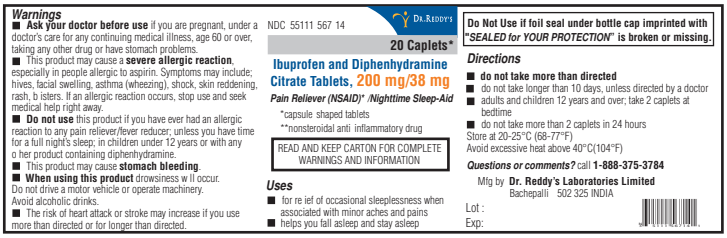
10 (b) (4) Liner utilized for tamper evident seal. (See container/closure above)

Date of Review: 6/25/09 **Date of Submission:** April 10, 2009

Primary Reviewer: J Barlow **Date:**

Team Leader: Koung Lee **Date:**

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 20's count
Actual Label Size: 95 mm x 30 mm



Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, b isters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any o her product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness w ll occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

NDC 55111 567 14

Dr. Reddy's

20 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)* /Nighttime Sleep-Aid

*capsule shaped tablets

**nonsteroidal anti inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for re ief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with "*SEALED for YOUR PROTECTION*" is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

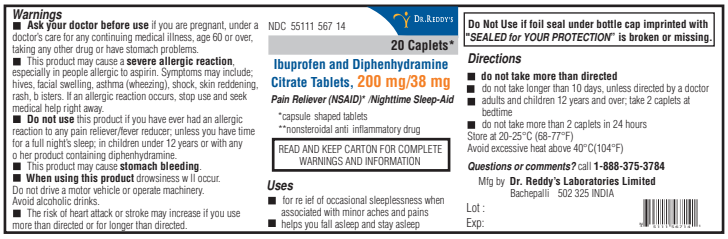
Mfg by **Dr. Reddy's Laboratories Limited**
Bachepalli 502 325 INDIA

Lot :

Exp:

(b) (4)

(b) (4)



Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, b isters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any o her product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness w ll occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

NDC 55111 567 14

Dr. Reddy's

20 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)* /Nighttime Sleep-Aid

*capsule shaped tablets

**nonsteroidal anti inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for re ief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with "*SEALED for YOUR PROTECTION*" is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

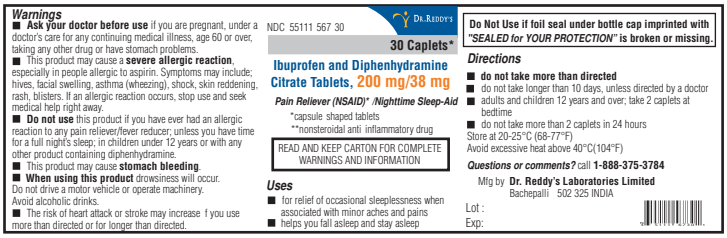
Questions or comments? call **1-888-375-3784**

Mfg by **Dr. Reddy's Laboratories Limited**
Bachepalli 502 325 INDIA

Lot :

Exp:

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 30's count
Actual Label Size: 95 mm x 30 mm



Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur.
Do not drive a motor vehicle or operate machinery.
Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase f you use more than directed or for longer than directed.

NDC 55111 567 30

Dr. Reddy's

30 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)* /Nighttime Sleep-Aid

*capsule shaped tablets
**nonsteroidal anti inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor
■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours
Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)

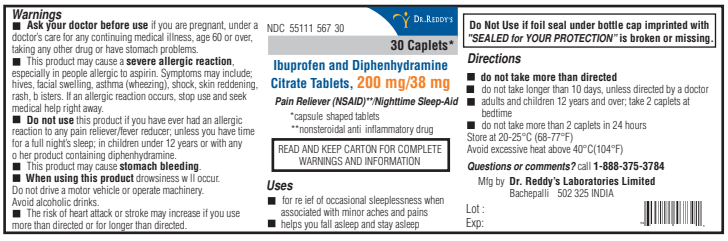
Questions or comments? call **1-888-375-3784**

Mfg by **Dr. Reddy's Laboratories Limited**
Bachepalli 502 325 INDIA

Lot :
Exp:

(b) (4)

(b) (4)



Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, b isters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any o her product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness w ll occur.
Do not drive a motor vehicle or operate machinery.
Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

NDC 55111 567 30

Dr. Reddy's

30 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule shaped tablets
**nonsteroidal anti inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for re ief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

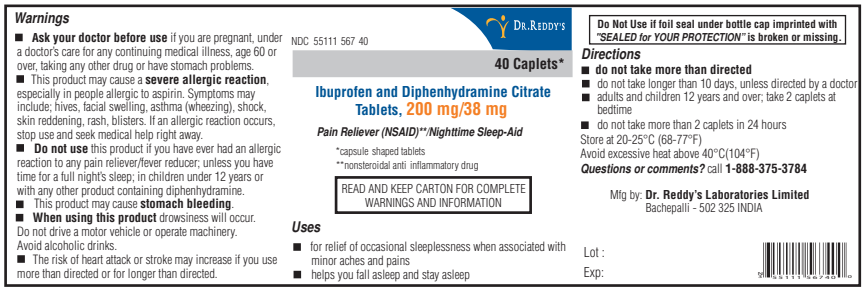
■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor
■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours
Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

Mfg by **Dr. Reddy's Laboratories Limited**
Bachepalli 502 325 INDIA

Lot :
Exp:

Final Container Label
Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg - 40's count
Actual Label Size: 113 mm x 37 mm



Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.
■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.
■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.
■ This product may cause **stomach bleeding**.
■ **When using this product** drowsiness will occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.
■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

DR. REDDY'S

NDC 55111 567 40

40 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule shaped tablets
**nonsteroidal anti inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor
■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours

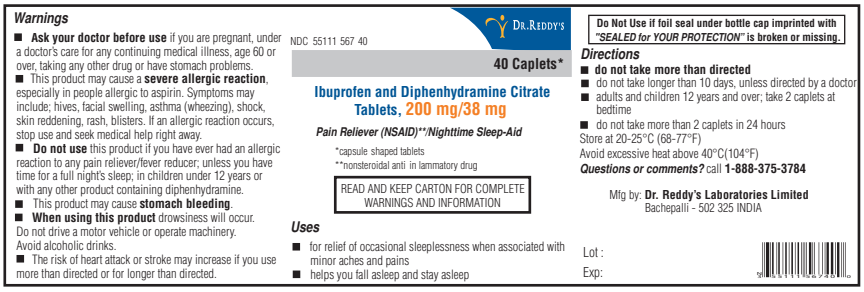
Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)
Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :
Exp:

(b) (4)

(b) (4)



Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.
■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.
■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.
■ This product may cause **stomach bleeding**.
■ **When using this product** drowsiness will occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.
■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

DR. REDDY'S

NDC 55111 567 40

40 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule shaped tablets
**nonsteroidal anti in lammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor
■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)
Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :
Exp:

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 80's count
Actual Label Size: 120 mm x 40 mm

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.
■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.
■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.
■ This product may cause **stomach bleeding**.
■ **When using this product** drowsiness will occur.
Do not drive a motor vehicle or operate machinery.
Avoid alcoholic drinks.
■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

DR. REDDY'S

NDC 55111-567-80

80 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets
**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor
■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours
Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)
Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :
Exp:

(b) (4)

(b) (4)

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.
■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.
■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.
■ This product may cause **stomach bleeding**.
■ **When using this product** drowsiness will occur.
Do not drive a motor vehicle or operate machinery.
Avoid alcoholic drinks.
■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

DR. REDDY'S

NDC 55111-567-80

80 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets
**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor
■ adults and children 12 years and over; take 2 caplets at bedtime
■ do not take more than 2 caplets in 24 hours
Store at 20-25°C (68-77°F)
Avoid excessive heat above 40°C(104°F)
Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :
Exp:

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 90's count
Actual Label Size: 135 mm x 50 mm

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

Dr. Reddy's

NDC 55111-567-90

90 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

(b) (4)

(b) (4)

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

Dr. Reddy's

NDC 55111-567-90

90 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 180's count
Actual Label Size: 145 mm x 60 mm

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

NDC 55111-567-18

DR.REDDY'S

180 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

(b) (4)

(b) (4)

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

NDC 55111-567-18

DR.REDDY'S

180 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments? call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

Final Container Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 500's count
Actual Label Size: 170 mm x 90 mm

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur.

Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

DR.REDDY'S

NDC 55111-567-05

500 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments?

call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

(b) (4)

(b) (4)

Warnings

■ **Ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems.

■ This product may cause a **severe allergic reaction**, especially in people allergic to aspirin. Symptoms may include; hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

■ **Do not use** this product if you have ever had an allergic reaction to any pain reliever/fever reducer; unless you have time for a full night's sleep; in children under 12 years or with any other product containing diphenhydramine.

■ This product may cause **stomach bleeding**.

■ **When using this product** drowsiness will occur.

Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks.

■ The risk of heart attack or stroke may increase if you use more than directed or for longer than directed.

DR.REDDY'S

NDC 55111-567-05

500 Caplets*

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)**/Nighttime Sleep-Aid

*capsule-shaped tablets

**nonsteroidal anti-inflammatory drug

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses

■ for relief of occasional sleeplessness when associated with minor aches and pains

■ helps you fall asleep and stay asleep

Do Not Use if foil seal under bottle cap imprinted with *"SEALED for YOUR PROTECTION"* is broken or missing.

Directions

■ **do not take more than directed**

■ do not take longer than 10 days, unless directed by a doctor

■ adults and children 12 years and over; take 2 caplets at bedtime

■ do not take more than 2 caplets in 24 hours

Store at 20-25°C (68-77°F)

Avoid excessive heat above 40°C(104°F)

Questions or comments?

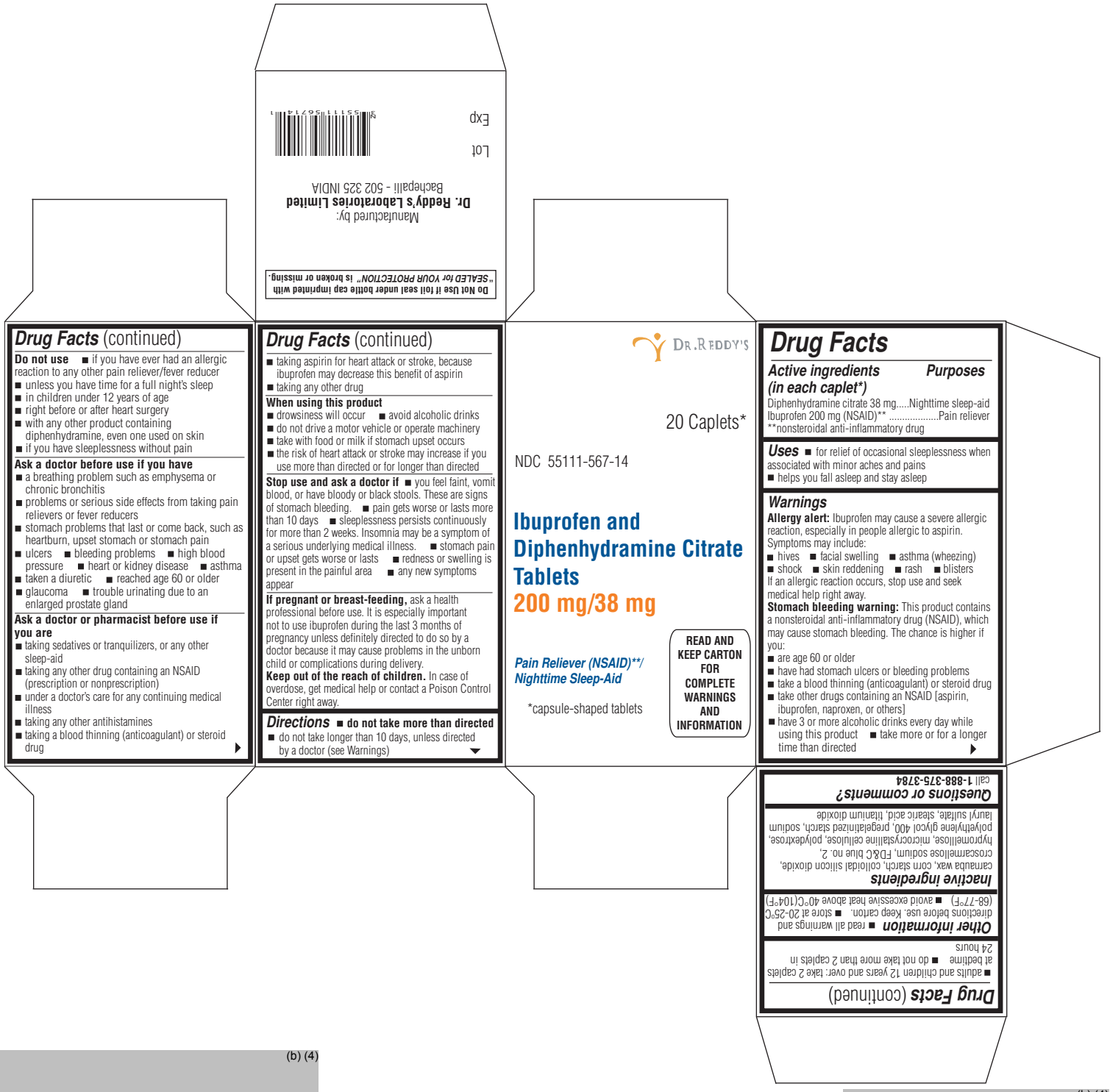
call **1-888-375-3784**

Mfg by: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Lot :

Exp:

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 20's count
Actual Label Size: 45 mm x 45 mm x 80 mm



Exp

Lot

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

Do Not Use if foil seal under bottle cap imprinted with "*SEALED for YOUR PROTECTION*" is broken or missing.

Drug Facts (continued)

Do not use ■ if you have ever had an allergic reaction to any other pain reliever/fever reducer
■ unless you have time for a full night's sleep
■ in children under 12 years of age
■ right before or after heart surgery
■ with any other product containing diphenhydramine, even one used on skin
■ if you have sleeplessness without pain

Ask a doctor before use if you have
■ a breathing problem such as emphysema or chronic bronchitis
■ problems or serious side effects from taking pain relievers or fever reducers
■ stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
■ ulcers ■ bleeding problems ■ high blood pressure ■ heart or kidney disease ■ asthma
■ taken a diuretic ■ reached age 60 or older
■ glaucoma ■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are
■ taking sedatives or tranquilizers, or any other sleep-aid
■ taking any other drug containing an NSAID (prescription or nonprescription)
■ under a doctor's care for any continuing medical illness
■ taking any other antihistamines
■ taking a blood thinning (anticoagulant) or steroid drug ▶

Drug Facts (continued)

■ taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
■ taking any other drug

When using this product
■ drowsiness will occur ■ avoid alcoholic drinks
■ do not drive a motor vehicle or operate machinery
■ take with food or milk if stomach upset occurs
■ the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

Stop use and ask a doctor if ■ you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. ■ pain gets worse or lasts more than 10 days ■ sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness. ■ stomach pain or upset gets worse or lasts ■ redness or swelling is present in the painful area ■ any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor (see Warnings) ▼

DR. REDDY'S

20 Caplets*

NDC 55111-567-14

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

Pain Reliever (NSAID)**/ Nighttime Sleep-Aid

*capsule-shaped tablets

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Drug Facts

Active ingredients (in each caplet*)	***Purposes***
Diphenhydramine citrate 38 mg	Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)**	Pain reliever

**nonsteroidal anti-inflammatory drug

Uses ■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
■ hives ■ facial swelling ■ asthma (wheezing)
■ shock ■ skin reddening ■ rash ■ blisters
If an allergic reaction occurs, stop use and seek medical help right away.
Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:
■ are age 60 or older
■ have had stomach ulcers or bleeding problems
■ take a blood thinning (anticoagulant) or steroid drug
■ take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
■ have 3 or more alcoholic drinks every day while using this product ■ take more or for a longer time than directed ▶

Questions or comments?
call **1-888-375-3784**

Inactive ingredients
carnauba wax, corn starch, colloidal silicon dioxide, croscarmellose sodium, FD&C blue no. 2, hypromellose, microcrystalline cellulose, polydextrose, polyethylene glycol 400, pregelatinized starch, sodium lauryl sulfate, stearic acid, titanium dioxide

Other information ■ read all warnings and directions before use. Keep carton. ■ Store at 20-25°C (68-77°F) ■ avoid excessive heat above 40°C(104°F)

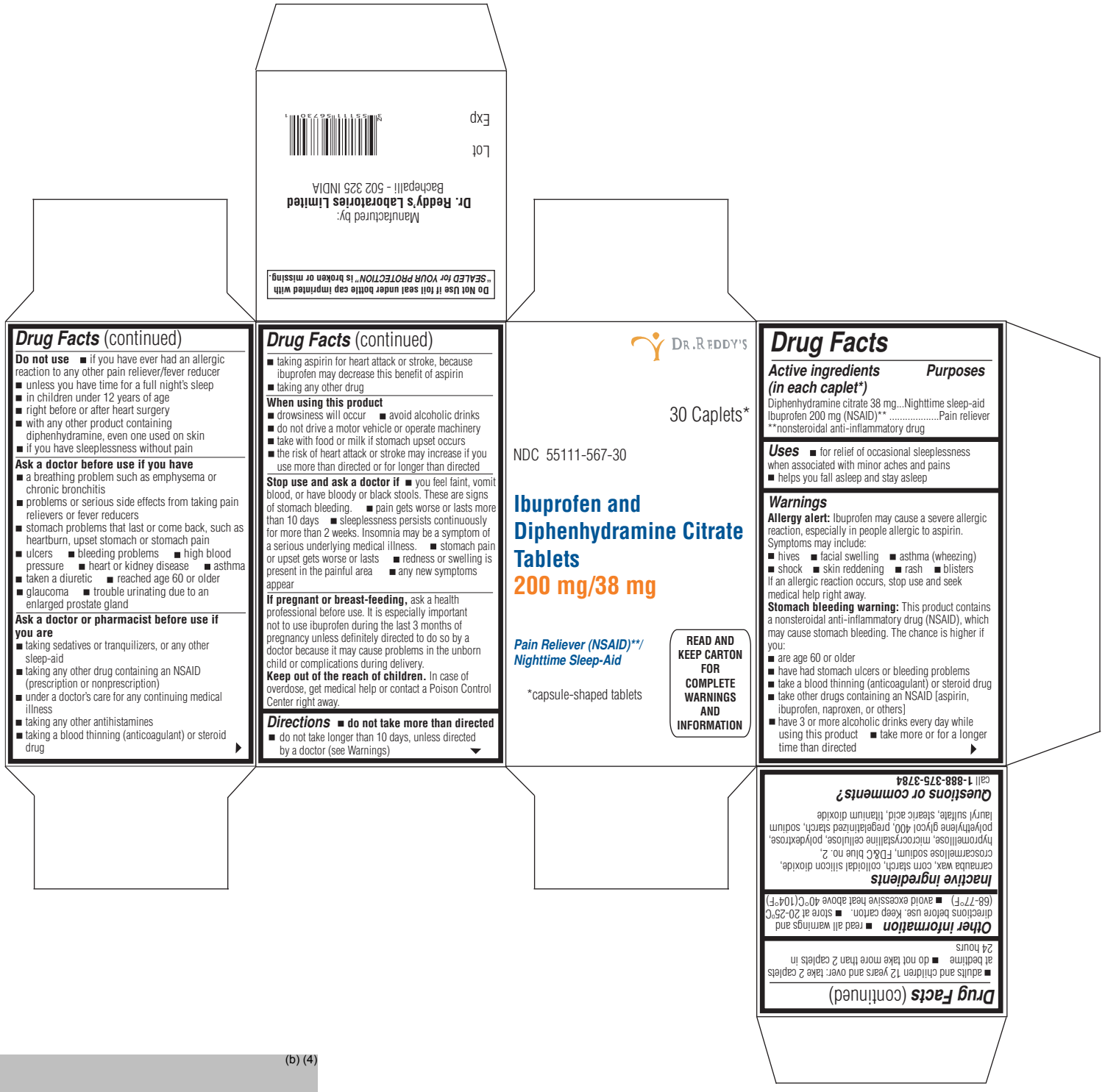
Drug Facts (continued)

■ adults and children 12 years and over: take 2 caplets at bedtime ■ do not take more than 2 caplets in 24 hours

(b) (4)

(b) (4)

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 30's count
Actual Label Size: 45 mm x 45 mm x 80 mm



Drug Facts (continued)

Do not use ■ if you have ever had an allergic reaction to any other pain reliever/fever reducer
■ unless you have time for a full night's sleep
■ in children under 12 years of age
■ right before or after heart surgery
■ with any other product containing diphenhydramine, even one used on skin
■ if you have sleeplessness without pain

Ask a doctor before use if you have
■ a breathing problem such as emphysema or chronic bronchitis
■ problems or serious side effects from taking pain relievers or fever reducers
■ stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
■ ulcers ■ bleeding problems ■ high blood pressure ■ heart or kidney disease ■ asthma
■ taken a diuretic ■ reached age 60 or older
■ glaucoma ■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are
■ taking sedatives or tranquilizers, or any other sleep-aid
■ taking any other drug containing an NSAID (prescription or nonprescription)
■ under a doctor's care for any continuing medical illness
■ taking any other antihistamines
■ taking a blood thinning (anticoagulant) or steroid drug

Drug Facts (continued)

■ taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
■ taking any other drug

When using this product
■ drowsiness will occur ■ avoid alcoholic drinks
■ do not drive a motor vehicle or operate machinery
■ take with food or milk if stomach upset occurs
■ the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

Stop use and ask a doctor if ■ you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. ■ pain gets worse or lasts more than 10 days ■ sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness. ■ stomach pain or upset gets worse or lasts ■ redness or swelling is present in the painful area ■ any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor (see Warnings)

DR. REDDY'S

30 Caplets*

NDC 55111-567-30

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

*Pain Reliever (NSAID)**/ Nighttime Sleep-Aid*

*capsule-shaped tablets

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Drug Facts

Active ingredients (in each caplet*)	Purposes
Diphenhydramine citrate 38 mg	Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)**	Pain reliever

**nonsteroidal anti-inflammatory drug

Uses ■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
■ hives ■ facial swelling ■ asthma (wheezing)
■ shock ■ skin reddening ■ rash ■ blisters
If an allergic reaction occurs, stop use and seek medical help right away.
Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:
■ are age 60 or older
■ have had stomach ulcers or bleeding problems
■ take a blood thinning (anticoagulant) or steroid drug
■ take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
■ have 3 or more alcoholic drinks every day while using this product ■ take more or for a longer time than directed

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

Lot

Exp

Do Not Use if foil seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

Drug Facts (continued)

Directions ■ adults and children 12 years and over: take 2 caplets at bedtime ■ do not take more than 2 caplets in 24 hours

Other information ■ read all warnings and directions before use. Keep carton. ■ store at 20-25°C (68-77°F) ■ avoid excessive heat above 40°C (104°F)

Inactive ingredients
carnauba wax, corn starch, colloidal silicon dioxide, croscarmellose sodium, FD&C blue no. 2, hypromellose, microcrystalline cellulose, polydextrose, polyethylene glycol 400, pregelatinized starch, sodium lauryl sulfate, stearic acid, titanium dioxide

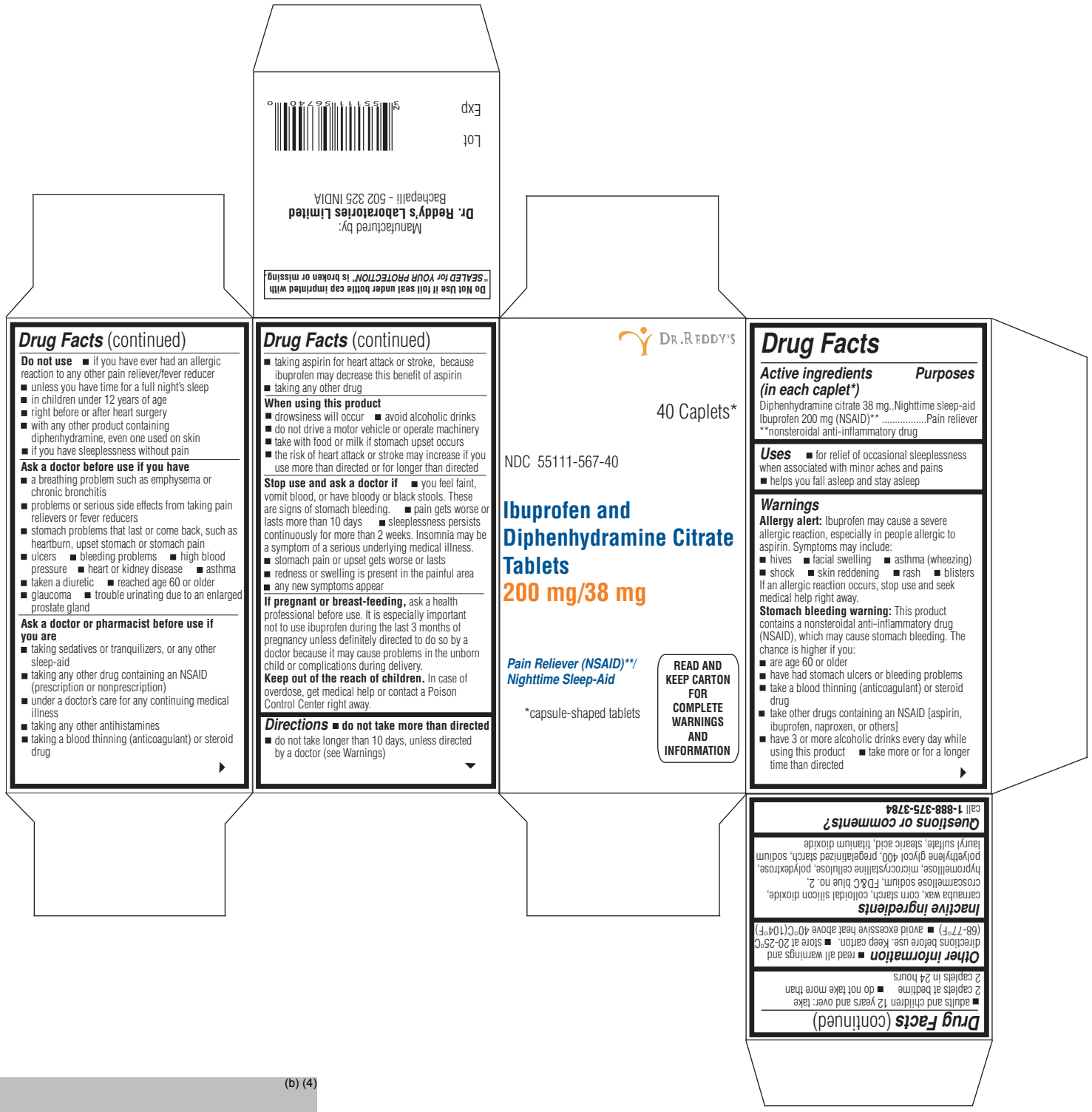
Questions or comments?
call 1-888-375-3784

(b) (4)

(b) (4)

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 40's count

Actual Label Size: 44 mm x 44 mm x 85 mm



Lot

Exp

Do Not Use if foil seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

Drug Facts (continued)

Do not use ■ if you have ever had an allergic reaction to any other pain reliever/fever reducer
■ unless you have time for a full night's sleep
■ in children under 12 years of age
■ right before or after heart surgery
■ with any other product containing diphenhydramine, even one used on skin
■ if you have sleeplessness without pain

Ask a doctor before use if you have
■ a breathing problem such as emphysema or chronic bronchitis
■ problems or serious side effects from taking pain relievers or fever reducers
■ stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
■ ulcers ■ bleeding problems ■ high blood pressure ■ heart or kidney disease ■ asthma
■ taken a diuretic ■ reached age 60 or older
■ glaucoma ■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are
■ taking sedatives or tranquilizers, or any other sleep-aid
■ taking any other drug containing an NSAID (prescription or nonprescription)
■ under a doctor's care for any continuing medical illness
■ taking any other antihistamines
■ taking a blood thinning (anticoagulant) or steroid drug

Drug Facts (continued)

■ taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
■ taking any other drug

When using this product
■ drowsiness will occur ■ avoid alcoholic drinks
■ do not drive a motor vehicle or operate machinery
■ take with food or milk if stomach upset occurs
■ the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

Stop use and ask a doctor if ■ you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. ■ pain gets worse or lasts more than 10 days ■ sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness.
■ stomach pain or upset gets worse or lasts
■ redness or swelling is present in the painful area
■ any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ **do not take more than directed**
■ do not take longer than 10 days, unless directed by a doctor (see Warnings)

DR. REDDY'S

40 Caplets*

NDC 55111-567-40

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

*Pain Reliever (NSAID)**/ Nighttime Sleep-Aid*

*capsule-shaped tablets

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Drug Facts

Active ingredients (in each caplet*) ***Purposes***
Diphenhydramine citrate 38 mg..Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)** .....Pain reliever
**nonsteroidal anti-inflammatory drug

Uses ■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
■ hives ■ facial swelling ■ asthma (wheezing)
■ shock ■ skin reddening ■ rash ■ blisters
If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:
■ are age 60 or older
■ have had stomach ulcers or bleeding problems
■ take a blood thinning (anticoagulant) or steroid drug
■ take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
■ have 3 or more alcoholic drinks every day while using this product ■ take more or for a longer time than directed

Drug Facts (continued)

■ adults and children 12 years and over: take 2 caplets at bedtime ■ do not take more than 2 caplets in 24 hours

Other information ■ read all warnings and directions before use. Keep carton. ■ store at 20-25°C (68-77°F) ■ avoid excessive heat above 40°C(104°F)

Inactive ingredients
carnauba wax, corn starch, colloidal silicon dioxide, croscarmellose sodium, FD&C blue no. 2, hypromellose, microcrystalline cellulose, polydextrose, polyethylene glycol 400, pregelatinized starch, sodium lauryl sulfate, stearic acid, titanium dioxide

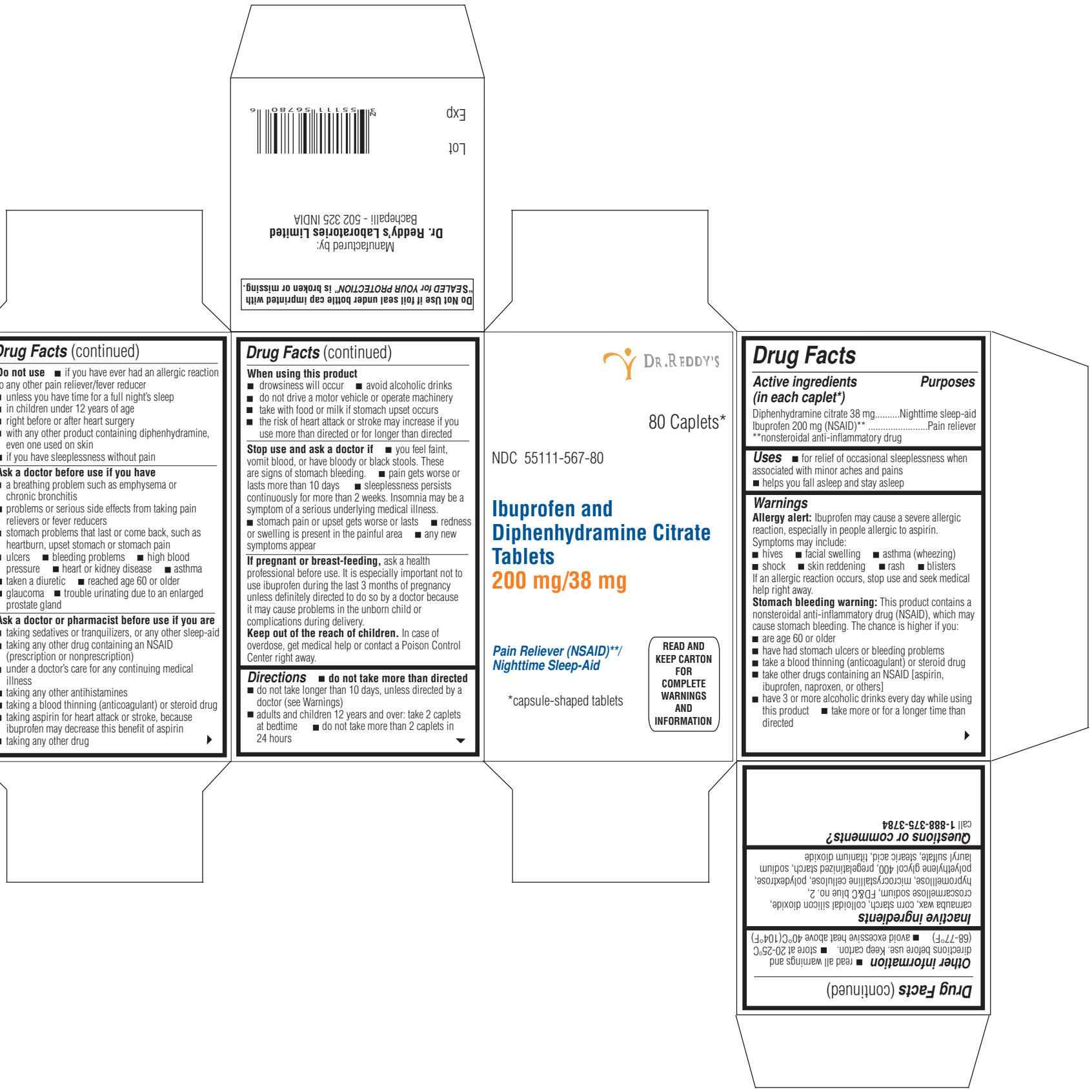
Questions or comments?
call **1-888-375-3784**

(b) (4)

(b) (4)

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 80's count

Actual Label Size: 52 mm x 52 mm x 88 mm

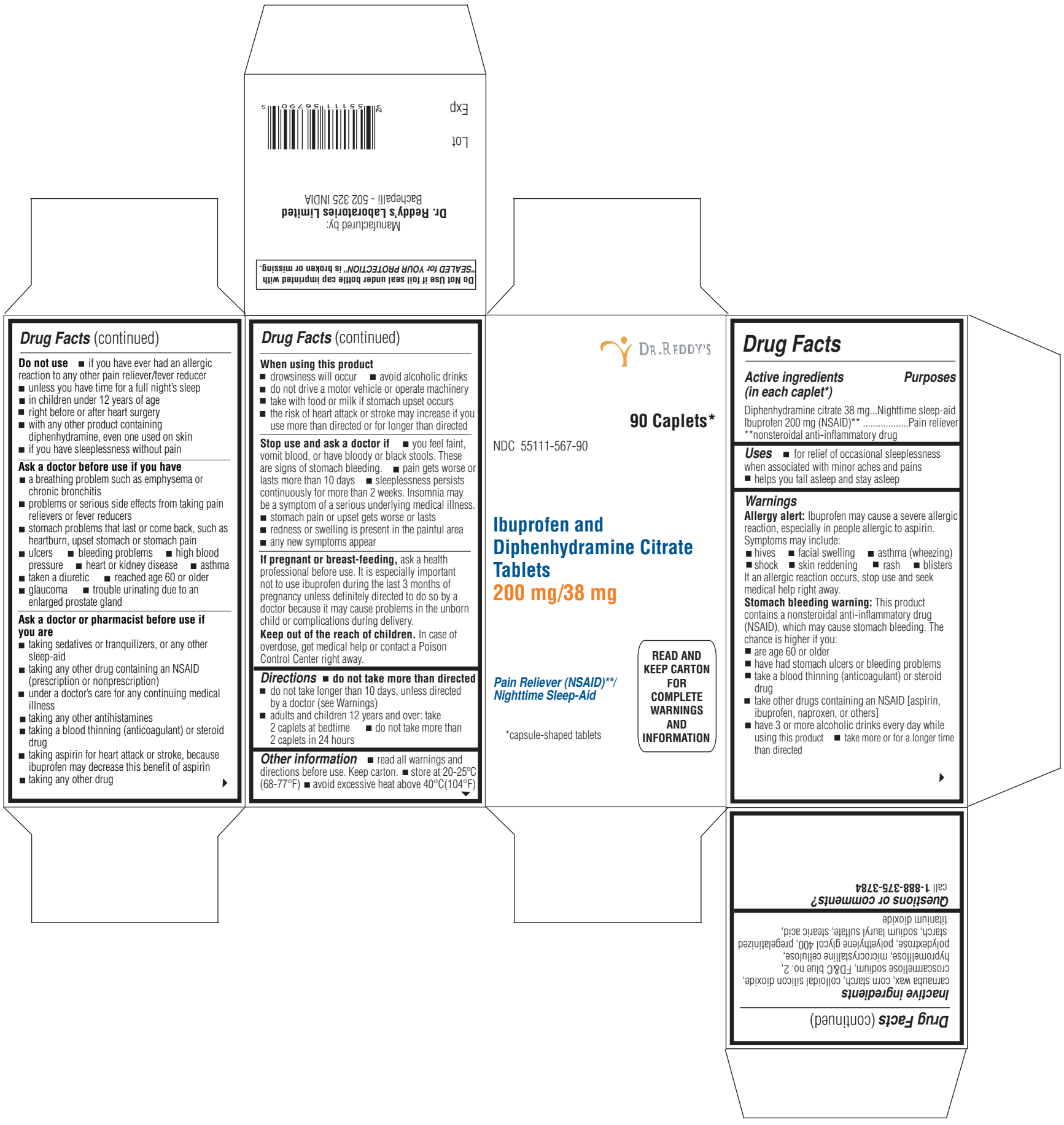


(b) (4)

(b) (4)

NOTE: This Container Carton is fit to paper print

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 90's count
Actual Label Size: 52 mm x 52 mm x 106 mm



(b) (4)

(b) (4)

NOTE: This Container Carton is fit to paper print

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 180's count

Actual Label Size: 60 mm x 60 mm x 126 mm

Lot

Exp

Do Not Use if foil seal under bottle cap imprinted with "SEALED for YOUR PROTECTION" is broken or missing.

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

Drug Facts (continued)

- with any other product containing diphenhydramine, even one used on skin
- if you have sleeplessness without pain

Ask a doctor before use if you have

- a breathing problem such as emphysema or chronic bronchitis
- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
- ulcers ■ bleeding problems ■ high blood pressure ■ heart or kidney disease ■ asthma
- taken a diuretic ■ reached age 60 or older
- glaucoma ■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are

- taking sedatives or tranquilizers, or any other sleep-aid
- taking any other drug containing an NSAID (prescription or nonprescription)
- under a doctor's care for any continuing medical illness
- taking any other antihistamines
- taking a blood thinning (anticoagulant) or steroid drug
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product

- drowsiness will occur ■ avoid alcoholic drinks
- do not drive a motor vehicle or operate machinery
- take with food or milk if stomach upset occurs
- the risk of heart attack or storke may increase if you use more than directed or for longer than directed

Drug Facts (continued)

Stop use and ask a doctor if ■ you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. ■ pain gets worse or lasts more than 10 days ■ sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness.

- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ **do not take more than directed**

- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 2 caplets at bedtime ■ do not take more than 2 caplets in 24 hours

Other information ■ read all warnings and directions before use. Keep carton. ■ store at 20-25°C (68-77°F) ■ avoid excessive heat above 40°C(104°F)

Inactive ingredients

carnauba wax, corn starch, colloidal silicon dioxide, croscarmellose sodium, FD&C blue no. 2, hypromelllose, microcrystalline cellulose, polydextrose, polyethylene glycol 400, pregelatinized starch, sodium lauryl sulfate, stearic acid, titanium dioxide

Questions or comments?
call **1-888-375-3784**

DR. REDDY'S

180 Caplets*

NDC 55111-567-18

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

Pain Reliever (NSAID)**/ Nighttime Sleep-Aid

*capsule-shaped tablets

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Drug Facts

Active ingredients (in each caplet*) — ***Purposes***

Diphenhydramine citrate 38 mg...Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)** .....Pain reliever
**nonsteroidal anti-inflammatory drug

Uses ■ for relief of occasional sleeplessness when associated with minor aches and pains
■ helps you fall asleep and stay asleep

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- hives ■ facial swelling ■ asthma (wheezing)
- shock ■ skin reddening ■ rash ■ blisters

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product ■ take more or for a longer time than directed

Do not use ■ if you have ever had an allergic reaction to any other pain reliever/fever reducer

- unless you have time for a full night's sleep
- in children under 12 years of age
- right before or after heart surgery

(b) (4)

(b) (4)

NOTE: This Container Carton is fit to paper print

Final Container Carton Label
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg - 500's count
Actual Label Size: 82 mm x 82 mm x 160 mm

Exp

Lot

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

Do Not Use if foil seal under bottle cap imprinted with "*SEALED for YOUR PROTECTION*" is broken or missing.

Drug Facts (continued)

Ask a doctor before use if you have
- a breathing problem such as emphysema or chronic bronchitis
- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
- ulcers ■ bleeding problems ■ high blood pressure ■ heart or kidney disease ■ asthma
- taken a diuretic ■ reached age 60 or older
- glaucoma ■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are
- taking sedatives or tranquilizers, or any other sleep-aid
- taking any other drug containing an NSAID (prescription or nonprescription)
- under a doctor's care for any continuing medical illness
- taking any other antihistamines
- taking a blood thinning (anticoagulant) or steroid drug
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product
- drowsiness will occur ■ avoid alcoholic drinks
- do not drive a motor vehicle or operate machinery
- take with food or milk if stomach upset occurs
- the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

Stop use and ask a doctor if ■ you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. ■ pain gets worse or lasts more than 10 days ■ sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness.

Drug Facts (continued)

- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ do not take more than directed
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 2 caplets at bedtime ■ do not take more than 2 caplets in 24 hours

Other information ■ read all warnings and directions before use. Keep carton. ■ store at 20-25°C (68-77°F) ■ avoid excessive heat above 40°C(104°F)

Inactive ingredients
carnauba wax, corn starch, colloidal silicon dioxide, croscarmellose sodium, FD&C blue no. 2, hypromelllose, microcrystalline cellulose, polydextrose, polyethylene glycol 400, pregelatinized starch, sodium lauryl sulfate, stearic acid, titanium dioxide

Questions or comments?
call **1-888-375-3784**

DR. REDDY'S

500 Caplets*

NDC 55111-567-05

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

Pain Reliever (NSAID)**/
Nighttime Sleep-Aid

*capsule-shaped tablets

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Drug Facts

Active ingredients (in each caplet*) — ***Purposes***
Diphenhydramine citrate 38 mg.....Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)** .....Pain reliever
**nonsteroidal anti-inflammatory drug

Uses ■ for relief of occasional sleeplessness when associated with minor aches and pains
- helps you fall asleep and stay asleep

Warnings
Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
- hives ■ facial swelling ■ asthma (wheezing)
- shock ■ skin reddening ■ rash ■ blisters

If an allergic reaction occurs, stop use and seek medical help right away.
Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:
- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product ■ take more or for a longer time than directed

Do not use ■ if you have ever had an allergic reaction to any other pain reliever/fever reducer
- unless you have time for a full night's sleep
- in children under 12 years of age
- right before or after heart surgery
- with any other product containing diphenhydramine, even one used on skin
- if you have sleeplessness without pain

(b) (4)

(b) (4)

NOTE: This Container Carton is fit to paper print

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Barlow
6/25/2009 09:48:12 AM
LABELING REVIEWER

Koung Lee
6/25/2009 02:35:48 PM
LABELING REVIEWER
For Wm Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	90-619
Date of Submission:	June 13, 2008 **and** December 26, 2008
Applicant's Name:	Dr. Reddys Laboratories
Established Name:	Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

---

Labeling Deficiencies:

1. CONTAINER/CARTON-

a. **General Comments -** Please note that the term "caplet" is not an official USP dosage form classification. Therefore, revise the name of your drug product to read as written below to be in accordance with USP 23. The term "caplet" may be retained in the net quantity statement as long as it is defined as a "capsule-shaped tablet".

b. Front Panel –
Revise to read as follows –

Dr. Reddy's
xx Caplets*
NDC#

Ibuprofen and
Diphenhydramine Citrate
Tablets
200 mg/38 mg

Pain Reliever (NSAID)/**
Nighttime Sleep-Aid

***capsule-shaped tablets**

c. Side Panel –

Active ingredients (in each caplet*)	Purposes
Diphenhydramine citrate 38 mg……..	Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)**	Pain reliever

**nonsteroidal anti-inflammatory drug

d. Please revise labels and labeling to be in accord with the most recently approved labeling for the reference listed drug, Advil PM® (NDA 21-394/S-012; approved June 12, 2008).

e. Please confirm that the correct font size was utilized in the text of your labels and labeling. We refer you to 21 CFR 201.66(d) for guidance referencing OTC format requirements.

f. We note that your proposed 180 and 500 count bottles utilize a non-CRC closure system. As noted in the Consumer Product Safety Commission 16 CFR; part 1700, OTC drug products need to utilize a CRC closure system. Please revise and/or comment.

2. **CONTAINERS – All strengths**

Increase the established name and drug strength to be the most prominent print on the label.

Revise your labeling as requested above and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

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 the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

FOR THE RECORD:

1. Carton/Container Labeling
   The model labeling used by the firm for Advil PM® was approved December 21, 2005; (N 21-394; approved December 21, 2005). This is not the most recently approved labeling. More recently approved labeling for the reference listed drug was approved June 12, 2008 (NDA 21-394/S-010).

2. Storage/Dispensing Conditions:
   NDA: Store at 20º-25ºC(68º-77ºF). Avoid excessive heat above 40°C (104°F).
   ANDA: Store at 20-25°C (68-77°F). Avoid excessive heat above 40°C (104°F).

3. Product Line:
   RLD – 2, 4, 20, 40, 80 and 180 count container/carton
   ANDA – 20, 30, 40, 80, 90, 180 and 500s

4. Inactive Ingredients:
   The listing of the inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition statement. **(Satisfactory per chemistry review listed below)**

Description and Composition of the Drug Product

What are the components and composition of the final product? What is the function(s) of each excipient? See the following tables. Satisfactory.

Quantitative Composition of Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg

S. No.	Component	Quantity per unit (mg)	% (w/w)	Pharmaceutical Function
	Granulation			
1.	Ibuprofen USP	200.00	(b) (4)	Active Pharmaceutical Ingredient

(b) (4)

(b) (4)

5. Container/Closure: We question the 180 count & 500 count bottle since they do NOT utilize a CRC closure. (Se comments above)

What container closure system(s) is proposed for packaging and storage of the drug product? See the packaging information provided, below. The proposed container/closure systems comply with USP <661> and USP <671> requirements, and all components used in these container/closure systems have been used in approved FDA products (see section 3.2.P.2.4.). **Satisfactory.**
The firm has provided certificate of compliance (under part 177.1520, see section 3.2.P.7) for the LDPE bags used in contact with the drug product. **Satisfactory.**

Ibuprofen and Diphenhydramine citrate caplets 200/38 mg:

Container Packaging:

Package Size	Configuration
20's	• (b) (4) • • • Container label
30's	• (b) (4) • • • Container label
40's	• (b) (4) • • • Container label
80's	• (b) (4) • • • Container label
90's	• (b) (4) • • • Container label
180's	• (b) (4) • • • Container label
500's	• (b) (4) • • • Container label

6. All manufacturing will be performed by:
   Dr Reddy's Laboratories Limited,
   Jeedimetla
   Hyderabad, Andhra Pradesh,
   India-500005

7. Tablet (Caplet) Description: Scoring configuration is the same as the RLD scoring. Neither tablet is scored-

   Blue colored, capsule shaped, biconvex, film coated tablets debossed 'RDY' on one side and '565' on the other side.

8. Patent/Exclusivity Data:
   Patent Information: Firm filed paragraph III but exclusivity expired in December 2008.

Patent Data: NDA 21-394

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	***None***	None	None	None	None

Exclusivity Data: NDA 21-394

Code	Reference	Expiration	Labeling Impact
None	No exclusivities	None	None

5. **Revisions needed post-approval**; None

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Advil PM®
NDA Number: N 21-394
NDA Drug Name: Advil PM®
NDA Firm: N 21-394/S-010; Approved June 12, 2008
Date of Approval of NDA Insert and supplement: N 21-394/S-010; Approved June 12, 2008
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container: Most recently approved labeling of the reference listed drug, Advil PM®.

Date of Review: 3/17/09 **Date of Submission: June 13, 2008 and December 26, 2008**
Primary Reviewer: Jim Barlow **Date:**

Team Leader: Koung Lee **Date:**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Barlow
3/18/2009 01:56:51 PM
LABELING REVIEWER

James Barlow
3/18/2009 01:59:16 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-619

CHEMISTRY REVIEWS

ANDA 90-619

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

Dr. Reddy's Laboratories, Ltd

Yusuf Amin
OGD – Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 90-619

2. REVIEW #: 2

3. REVIEW DATE: 26-FEB-2009

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	13-JUN-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	30-DEC-2008
Amendment	29-JAN-2009
Amendment	26-FEB-2009

NAME & ADDRESS OF APPLICANT:

Name:	Dr. Reddy's Laboratories, Ltd
Address:	Generics Division Bachepalli 502 325 Andhra Pradesh, India U.S. Agent Dr. Reddy's Laboratories Inc. 200 Somerset Corporate Blvd, 7th Floor Bridgewater, NJ 08807
Representative:	Kumara Sekar
Telephone: Fax:	704-496-6065 704-496-6082

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) USAN Name: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Advil® PM caplets manufactured by Wyeth Consumer Healthcare NDA # 21-394.
There is no unexpired patent for this product.

There is no unexpired exclusivity for this product in the electronic Orange Book.

Reddy's certifies that it will not market the product until the exclusivity expires on 21-DEC-2008.

10. PHARMACOL. CATEGORY: For relief of occasional sleeplessness when associated with minor aches and pains. Aids in falling asleep and staying asleep.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 200 mg/38 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __Rx _X__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____X__Not a SPOTS product

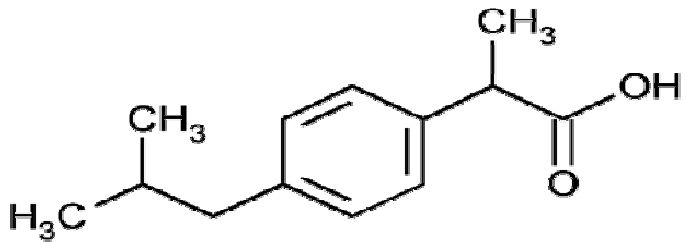
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ibuprofen: $C_{13}H_{18}O_2$: M.W. 206.28

Chemical Name(s): Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-.
(±)-p-Isobutylhydratropic acid.
(±)-2-(p-Isobutylphenyl)propionic acid

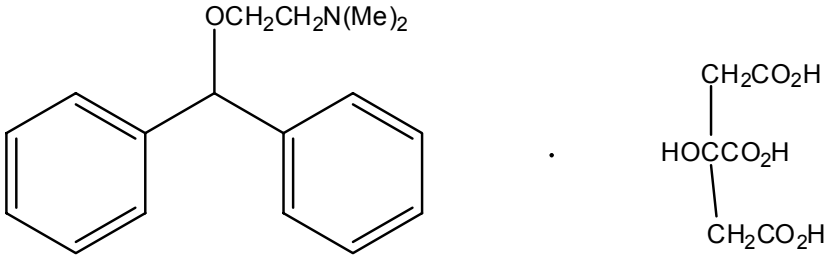
CAS#: 15687-27-1

Molecular Structure:



Diphenhydramine Citrate: $C_{17}H_{21}NO \cdot C_6H_8O_7$ M.W. 491.06
Chemical Name: Ethanamine, 2-(diphenylmethoxy)-N,N-dimethyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).
2-(Diphenylmethoxy)-N,N-dimethylethylamine citrate (1:1)

CAS#: 88637-37-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
6669	II	Reddy's Laboratories	Ibuprofen (API)	3	Adequate.	11-FEB-2008	Reviewed by: R. Powers
[redacted] (b) (4)				1	Adequate	26-FEB-2009	Reviewed by: Y. Amin
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[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Advil® PM Ibuprofen/Diphenhydramine Citrate Tablets 200/38 mg	21-394	RLD

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12-NOV-2008	S. Adams
Methods Validation	N/A		
Labeling	Acceptable	25-JUNE-2009	J. Barlow
Bioequivalence	Acceptable	08-MAY-2009	G. Johnson
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-619
The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC, Labeling, Bio and EER are Approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance Ibuprofen: White or off-white crystalline powder. Freely soluble in ethanol, acetone, chloroform or ethyl ether; insoluble in water Practically insoluble in water. Ibuprofen USP does not exhibit any polymorphism.

Drug Substance Diphenhydramine Citrate: White crystalline powder. Slightly soluble in water and alcohol; insoluble in toluene and acetone.

The drug product: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg are for oral administration.

B. Description of How the Drug Product is Intended to be Used

Oral tablet is for relief of occasional sleeplessness when associated with minor aches and pains. Aids in falling asleep and staying asleep an Anti-hypertension drug. The recommended maximum daily dosage is 2 tablets in 24 hours, (400 mg of Ibuprofen and 76 mg of Diphenhydramine Citrate).

C. Basis for Approvability or Not-Approval Recommendation

The CMC, Labeling, Bio and EER are Approvable.

32 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

Yusuf A. Amin
7/8/2009 07:42:13 AM
CHEMIST

Albert Mueller
7/8/2009 09:20:24 AM
CHEMIST

Dat Doan
7/9/2009 07:47:19 AM
CSO

ANDA 90-619

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

Dr. Reddy's Laboratories, Ltd

Yusuf Amin
OGD – Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 90-619

2. REVIEW #: 1

3. REVIEW DATE: 25-SEP-2008

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	13-JUN-2008

NAME & ADDRESS OF APPLICANT:

Name:	Dr. Reddy's Laboratories, Ltd
Address:	Generics Division Bachepalli 502 325 Andhra Pradesh, India U.S. Agent Dr. Reddy's Laboratories Inc. 200 Somerset Corporate Blvd, 7th Floor Bridgewater, NJ 08807
Representative:	Kumara Sekar
Telephone: Fax:	908-203-4937 908-203-4980

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) USAN Name: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg

9. LEGAL BASIS FOR SUBMISSION:

   The RLD is Advil® PM caplets manufactured by Wyeth Consumer Healthcare NDA # 21-394.
   There is no unexpired patent for this product.

There is an unexpired exclusivity for this product in the electronic Orange Book.
Exclusivity NC (New Combination) Expiry date 21-DEC-2008.

Reddy's certifies that it will not market the product until the exclusivity expires on 21-DEC-2008.

10. PHARMACOL. CATEGORY: For relief of occasional sleeplessness when associated with minor aches and pains. Aids in falling asleep and staying asleep.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 200 mg/38 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __Rx _X__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

____X__Not a SPOTS product

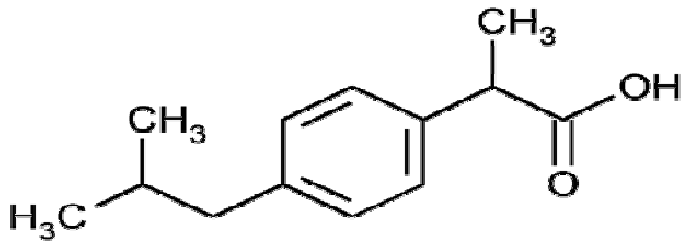
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ibuprofen: $C_{13}H_{18}O_2$: M.W. 206.28

Chemical Name(s): Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-.
(±)-p-Isobutylhydratropic acid.
(±)-2-(p-Isobutylphenyl)propionic acid

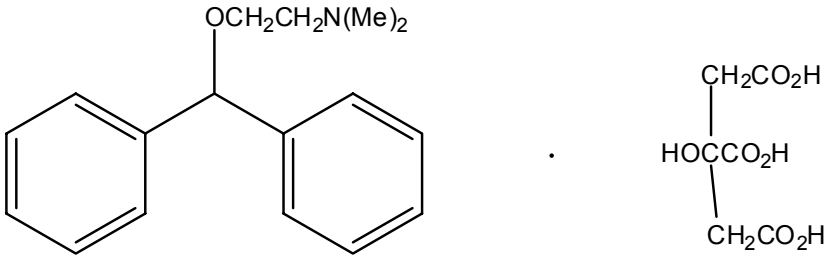
CAS#: 15687-27-1

Molecular Structure:



Diphenhydramine Citrate: $C_{17}H_{21}NO \cdot C_6H_8O_7$ M.W. 491.06
Chemical Name: Ethanamine, 2-(diphenylmethoxy)-N,N-dimethyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).
2-(Diphenylmethoxy)-N,N-dimethylethylamine citrate (1:1)

CAS#: 88637-37-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
6669	II	Reddy's	Ibuprofen (API)	3	Adequate.	11-FEB-2008	Reviewed by: R. Powers
[redacted]			(b) (4)	1	Inadequate	25-SEP-2008	Reviewed by: Y. Amin
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[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Advil® PM Ibuprofen/Diphenhydramine Citrate Tablets 200/38 mg	21-394	RLD

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-619
The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is NOT APPROVABLE at this stage. The deficiencies are listed in the letter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance Ibuprofen: White or off-white crystalline powder. Freely soluble in ethanol, acetone, chloroform or ethyl ether; insoluble in water Practically insoluble in water. Ibuprofen USP does not exhibit any polymorphism.

Drug Substance Diphenhydramine Citrate: White crystalline powder. Slightly soluble in water and alcohol; insoluble in toluene and acetone.

The drug product: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg are for oral administration.

B. Description of How the Drug Product is Intended to be Used

Oral tablet is for relief of occasional sleeplessness when associated with minor aches and pains. Aids in falling asleep and staying asleep an Anti-hypertension drug. The recommended maximum daily dosage is 2 tablets in 24 hours, (400 mg of Ibuprofen and 76 mg of Diphenhydramine Citrate).

C. Basis for Approvability or Not-Approval Recommendation

The application is NOT APPROVABLE at this stage. The deficiencies are listed in the letter.

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/s/

Yusuf A. Amin
11/21/2008 10:04:37 AM
CHEMIST

Rosario DCosta
11/21/2008 10:11:53 AM
CHEMIST

Dat Doan
11/21/2008 01:10:42 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-619

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	90-619	
Drug Product Name	Ibuprofen /Diphenhydramine Citrate Caplets (OTC)	
Strength(s)	200 mg /38 mg	
Applicant Name	Dr. Reddy's Laboratories Limited	
Address	Mailing Address: Bachepalli, Post Bag No. 15, Kukatpally P.O., Hyderabad - 500 072, India. Factory Address: Bachepalli 502 325, India	
Applicant's Point of Contact	Kumara Sekar, Ph.D., Sr.Director, Global Regulatory Affairs & Compliance	
Contact's Telephone Number	704-496-6065	
Contact's Fax Number	704-496-6082	
Original Submission Date(s)	June 13, 2008	
Submission Date(s) of Amendment(s) Under Review	April 17, 2009	
Reviewer	Glendolynn S. Johnson, Pharm.D.	
Study Number (s)	149-07	155-07
Study Type (s)	Fasting	Non-Fasting
Strength (s)	200 mg/ 38 mg	200 mg/ 38 mg
Clinical Site	GVK BIOSCIENCES PVT LTD.	
Clinical Site Address	Clinical Pharmacology Unit 7th Floor, Swarna Jayanthi Commercial Complex Ameerpet, Hyderabad – 500 038	
Analytical Site	(b) (4)	
Analytical Site Address		
OUTCOME DECISION	Acceptable	

Review of an Amendment

1 EXECUTIVE SUMMARY

In this amendment, the firm, Dr. Reddy's Laboratories Limited, submitted its response to the deficiency letter dated April 15, 2009 from the Division of Bioequivalence (DBE) for its proposed drug product, Ibuprofen /Diphenhydramine Citrate Caplets (OTC), 200 mg/ 38 mg. In response to the deficiency letter, the firm has submitted clarification on all the discrepancies identified by the reviewer concerning the different datasets for the *90% Confidence Intervals* on the fed study. The firm also submitted supportive documents. The firm was also asked to acknowledge the agency's comment on the dissolution

method and specification. The firm's responses to the deficiency comments are acceptable. The fed BE study No. 155-07 is now acceptable.

No Division of Scientific Investigations (DSI) inspection is pending or necessary. Both clinical and analytical sites were inspected on 10/26/2007.

This application is **acceptable.**

Background[1]

On June 13, 2008, the firm submitted two (2) single dose, two-way crossover, *in vivo* BE studies under fasted (1) and fed (1) conditions comparing its test product, Ibuprofen/ Diphenhydramine Citrate Caplets, 200 mg/38 mg, to the RLD product, Advil PM® (Ibuprofen/ Diphenhydramine Citrate) Caplets, 200 mg/38 mg, in healthy adult male subjects. The fed BE study was incomplete due to the following reason:

1. The firm has submitted two (2) different sets of 90% CI data for **diphenhydramine** in the fed study (155-07). The 90% CI values submitted in the firm's **Table 3**: Statistical Summary of the Comparative Bioavailability Data of 155-07 (Fed study) were inconsistent with the 90% CI data submitted in the study report (page 484), which is the firm's statistical analysis of diphenhydramine in the fed study. The firm was advised to explain this discrepancy.

[1] Division of System Files v 2.0. ANDA 90-619. Bioequivalence Review. N 090619 N 000 13-Jun-2008.

DBE Deficiency Comment No. 01

1. *You submitted two (2) different sets of 90% Confidence Interval (CI) summary data for diphenhydramine in the fed study (155-07). The 90% CI values you submitted in your **Table 3**: Statistical Summary of the Comparative Bioavailability Data of 155-07 (Fed study) are inconsistent with the 90% CI values submitted in your study report (page 484), which were based on your statistical analysis of diphenhydramine in the fed study. Please explain this discrepancy.*

Table 3: Statistical Summary of the Comparative Bioavailability Data of 155-07 (Fed study)

Ibuprofen + Diphenhydramine citrate 200 mg/38 mg caplets Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study No. 155-07)				
	Diphenhydramine			
AUC_{0-INF} (ng*h/mL)	381.6884	401.7938	95.00	89.84 - 100.45
AUC_{0-t} (ng*hr/mL)	354.9011	369.7046	96.00	98.84 - 106.29
C_{max} (ng/mL)	38.5564	40.0983	96.15	90.37 - 102.06

Project No.:155-07 15:07 Monday, May 26, 2008

Statistical Analysis for log transformed PK Parameters of Diphenhydramine

Pkpar	ISCV	lsm_T	lsm_R	Ratio	LCL	UCL	BIOEQUIVALENCE	Power
LnCmax	20.7	38.5564	40.0983	96.15	89.02	103.86	YES	99.9
LnAUC0-T	15.7	354.9011	369.7046	96.00	90.52	101.80	YES	100.0
LnAUC0-INF	14.9	381.6884	401.7938	95.00	89.84	100.45	YES	100.0

Firm's Response:

We acknowledge the Agency's comment. We regret for the typographical error in the 90% CI values of diphenhydramine in table 3 of the fed study (155-07). We have revised the table 3 to correct the values in line with the BE study report. The corrected 'table 3' is included in Module 2 and Module 5.

Table 3: Statistical Summary of the Comparative Bioavailability Data of 155-07 (Fed study)

Ibuprofen + Diphenhydramine citrate 200 mg/38 mg caplets Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No. 155-07)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
Diphenhydramine				
$AUC_{0\text{-}INF}$ (ng*h/mL)	381.6884	401.7938	95.00	89.84 - 100.45
$AUC_{0\text{-}t}$ (ng*hr/mL)	354.9011	369.7046	96.00	90.52 – 101.80
C_{max} (ng/mL)	38.5564	40.0983	96.15	89.02 – 103.86

DBE Comment

We acknowledge that you will conduct the dissolution testing using the following FDA-recommended method and specification:

The dissolution testing should be conducted in 900 mL of 50 mM Phosphate buffer, pH 6.5 at 37ºC ± 0.5ºC using USP apparatus 2 (paddle) at 50 rpm. The test product should meet the following specification: Not less than (b) (4) %(Q) of the labeled amount of both drugs (ibuprofen and diphenhydramine) in the dosage form is dissolved in 30 minutes.

Firm's Response:

We acknowledge the Agency's comment.

Reviewer's Comments:

1. The firm has acknowledged its acceptance of the FDA-recommended dissolution method of 900 mL of 50 mM Phosphate buffer, pH 6.5 at 37ºC ± 0.5ºC using USP apparatus 2 (paddle) at 50 rpm and specifications of Not less than (b) (4) %(Q) of the labeled amounts of both drugs (ibuprofen and diphenhydramine) in the dosage form are dissolved in 30 minutes.

2. The firm's responses to the deficiency comment No. 01 and DBE comment are acceptable.

Deficiency Comments:

None

Recommendations:

1. The Division of Bioequivalence finds the fasting BE study (149-07) acceptable. Dr. Reddy, conducted the fasting BE study on its test product, Ibuprofen / Diphenhydramine Caplet, 200 mg/ 38 mg , (lot # EC8063) comparing it to Wyeth's Advil PM® Caplet, 200 mg/ 38 mg (lot # B65608).

2. The Division of Bioequivalence finds the fed BE study (155-07) acceptable. Dr. Reddy conducted the fed BE study on its test product, Ibuprofen/ Diphenhydramine Caplet, 200 mg/ 38 mg, (lot # EC8063) comparing it to Wyeth's Advil PM® Caplet, 200 mg/ 38 mg (lot # B65608).

3. The firm's *in vitro* dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 50 mM Phosphate buffer, pH 6.5 at 37ºC ± 0.5ºC using USP apparatus 2 (paddle) at 50 rpm. The test product should meet the following specification(s): NLT (b)(4) % (Q) of both drug components in the dosage form is dissolved in 30 minutes.

4. This application is **acceptable.**

The firm should be informed of the above comment and recommendations.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-619

APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Ibuprofen/Diphenhydramine Citrate Caplets, 200 mg/38 mg (OTC)

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

We acknowledge you will conduct dissolution testing for the test product using the following FDA-recommended method and specifications:

The dissolution testing should be conducted in 900 mL of 50 mM Phosphate buffer, pH 6.5 at 37°C ± 0.5°C using USP apparatus 2 (paddle) at 50 rpm.

The test product should meet the following specifications:

Not less than (b)(4)% (Q) of the labeled amounts of both drugs (ibuprofen and diphenhydramine) in the dosage form are dissolved in 30 minutes.

Please note that the bioequivalence 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,

{See appended electronic signature page}

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

1.1 Outcome Page

ANDA: 90-619

2 *COMPLETED ASSIGNMENT FOR 90619 ID: 8197*

Reviewer: Johnson, Glendolynn **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Ibuprofen and Diphenhydramine Caplets (Dr. Reddy) Amendment

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Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
8197	4/22/2009	Other	Study Amendment Without Credit (WC)	0	0
				Bean Total:	0

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/s/

Glendolynn S Johnson
5/8/2009 08:33:38 AM
BIOPHARMACEUTICS

Yih Chain Huang
5/8/2009 10:22:32 AM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
5/8/2009 05:04:40 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	90-619	
Drug Product Name	Ibuprofen /Diphenhydramine Citrate Caplets (OTC)	
Strength(s)	200 mg /38 mg	
Applicant Name	Dr. Reddy's Laboratories Limited	
Address	Mailing Address: Bachepalli, Post Bag No. 15, Kukatpally P.O., Hyderabad - 500 072, India. Factory Address: Bachepalli 502 325, India	
Applicant's Point of Contact	Kumara Sekar, Ph.D., Sr.Director, Global Regulatory Affairs & Compliance	
Contact's Telephone Number	704-496-6065	
Contact's Fax Number	704-496-6082	
Original Submission Date(s)	June 13, 2008	
Submission Date(s) of Amendment(s) Under Review	December 12, 2008 (Long-term stability data) December 30, 2008 (Dissolution)	
Reviewer	Glendolynn S. Johnson, Pharm.D.	
Study Number (s)	149-07	155-07
Study Type (s)	Fasting	Non-Fasting
Strength (s)	200 mg/ 38 mg	200 mg/ 38 mg
Clinical Site	GVK BIOSCIENCES PVT LTD.	
Clinical Site Address	Clinical Pharmacology Unit 7th Floor, Swarna Jayanthi Commercial Complex Ameerpet, Hyderabad – 500 038	
Analytical Site	(b) (4)	
Analytical Site Address		
OUTCOME DECISION	**INCOMPLETE**	

1 EXECUTIVE SUMMARY

This application contains the results of the fasting and fed bioequivalence (BE) studies comparing the test product, Ibuprofen/ Diphenhydramine Citrate Caplets, 200 mg/ 38 mg, to the corresponding reference product, Advil PM® (ibuprofen/diphenhydramine citrate) Caplets, 200 mg/ 38 mg (OTC). It should be noted that the DBE recommends only the fasted study (measuring ibuprofen and diphenhydramine) for this drug product. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The firm's fasting study is acceptable and the fed study is incomplete due to discrepancies in the submission. The results are summarized in the tables below.

A. Ibuprofen

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Fasting Bioequivalence Study No. (149-07), N=40 (Male=40 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	68235.31	68066.99	1.00	98.01	102.54
AUC∞ (ng·hr/mL)	70526.44	70377.91	1.00	97.98	102.50
Cmax (ng/mL)	19353.31	18587.17	1.04	98.65	109.89

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Fed Bioequivalence Study No. (155-07), N=40 (Male=40 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	68165.01	66501.71	1.03	98.84	106.29
AUC∞ (ng·hr/mL)	71608.68	69166.27	1.04	99.82	107.38
Cmax (ng/mL)	15700.17	16347.86	0.96	90.37	102.06

B. Diphenhydramine

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Fasting Bioequivalence Study No. (149-07), N=40 (Male=40 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	306.84	304.96	1.01	94.75	106.84
AUC∞ (ng·hr/mL)	335.87	331.44	1.01	95.99	106.99
Cmax (ng/mL)	32.34	32.69	0.99	93.81	104.34

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Fed Bioequivalence Study No. (155-07), N=N1 (Male=40 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	354.90	369.70	0.96	90.52	101.80
AUC∞ (ng·hr/mL)	381.69	401.79	0.95	89.84	100.45
Cmax (ng/mL)	38.56	40.10	0.96	89.02	103.86

The firm also measured the active metabolite, Nor-Diphenhydramine, in both BE studies. In both BE studies, the pharmacokinetic (PK) parameters of the test and reference products for the active metabolite, Nor-Diphenhydramine, are comparable. Therefore, the metabolite data are supportive and are acceptable. For the fasting study, the Nor-Diphenhydramine results (point estimate, 90% CI) are: $LAUC_T$ of 1.00, 96.69 – 103.09%, $LAUC_\infty$ of 1.00, 97.02 – 102.15%, and LC_{max} of 0.96, 93.06 – 100.04%. For the fed study, the Nor-Diphenhydramine results (point estimate, 90% CI) are: $LAUC_T$ of 0.96, 92.11 – 100.88%, $LAUC_\infty$ of 0.95, 92.09 – 98.81%, and LC_{max} of 0.96, 92.35 – 100.73%.

The dissolution testing was reviewed previously (DFS: N 090619 N 000 13-Jun-2008). There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable. However, the firm's proposed specifications (NLT (b)(4)% (Q) in (b)(4) min) for both components were not acceptable. The firm acknowledged the FDA-recommended method and data driven specifications (NLT (b)(4)% (Q) in 30 minutes) for both components which the test product meets at the S1 level for both components on December 30, 2008.

No Division of Scientific Investigations (DSI) inspection is pending or necessary. Both clinical and analytical sites were inspected on 10/26/2007.

This application is **incomplete with deficiencies** in the fed study submission data.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Ibuprofen/Diphenhydramine Citrate Caplets, 200 mg/38 mg (OTC)
Reference Product	Advil PM® Caplets, 200 mg/38 mg. (OTC)
RLD Manufacturer	Wyeth Consumer Healthcare
NDA No.	21-394
RLD Approval Date	Approved December 21, 2005
Indication	Indicated to help with sleeplessness due to minor aches and pains. Diphenhydramine is an antihistamine that causes drowsiness and ibuprofen reduces inflammation and helps relieve minor aches and pains1 in adults and children ≥ 12 years old.

3.2 PK/PD Information

Bioavailability	Oral, immediate-release ibuprofen bioavailability (BA) is, at highest, 92% which indicates that it is well absorbed. The BA of the active form S (+) ibuprofen is highest following administration of the pure S (+) enantiomer. Racemic ibuprofen produces S (+) bioavailability of 71% and R (-) ibuprofen produces S (+) BA of 58%. Considerable R (-) ibuprofen is converted to S (+) ibuprofen *in vivo*[2]. Ibuprofen is approximately 80% absorbed from the gut[3]. Oral BA of diphenhydramine ranges from 65 – 100%2. Diphenhydramine is highly protein-bound[3]. With single doses up to 800 mg, a linear relationship exists between the amount of ibuprofen administered and the area under the curve. Above 800 mg, however, the area under the curve increases less than proportional to increases in dose. There is no evidence of drug accumulation or enzyme induction.[4]
Food Effect	Although the peak concentration is lower and time to peak concentration is slower if the drug is taken with food, the extent of ibuprofen absorption is not affected[3]. No food effect for diphenhydramine or ibuprofen is listed in the labeling.
Tmax	Peak concentrations of ibuprofen are reached at roughly 120 minutes following tablet administration[3]. Peak concentrations of diphenhydramine are reached within 2-4 hours[3].
Metabolism	Ibuprofen does undergo hepatic metabolism through oxidation by cytochrome

[1] www.drugdigest.org
[2] www.csi micromedex.com
[3] http://www.clinicalpharmacology-ip.com – Diphenhydramine; Ibuprofen
[4] www.rxlist.com/cgi/generic/ibup_cp.htm

	P450 2C9 to two inactive metabolites[3]. Diphenhydramine metabolism occurs in the liver to produce mainly diphenylmethoxyacetic acid, which then becomes conjugated; other metabolites are also formed. Diphenhydramine's metabolites include diphenylmethane (inactive), N,N-dimethyl-diphenhydramine (inactive), N,N-di-demethyl-diphenhydramine (inactive), diphenylmethoxy acetic acid (inactive), monodesmethyldiphenhydramine (inactive). Approximately 50% of diphenhydramine is metabolized in the liver to diphenylmethane, which suggests a large first-pass effect[3].
Excretion	Ibuprofen is excreted in the urine, 50 – 60% as metabolites and approximately 10% as unchanged drug. Some biliary excretion may occur[3]. Approximately 37% of the dose is excreted in 24 hours as metabolite 2-(p-(2carboxy-propyl)phenyl) propionic acid and 25% as metabolite2-(p-(2hydroxymethyl-propyl)phenyl) propionic acid[2]. Little, if any, diphenhydramine is excreted unchanged in urine. Metabolites of diphenhydramine are reported to be eliminated less rapidly than unchanged drug with 50 to 65% if these compounds recovered in the urine as diphenylmethane derivatives. Urinary excretion of total diphenhydramine metabolites represented 64% of a dose in single dose studies and 49% after multiple doses[3]. Most unchanged drug and metabolites are excreted within 24 hours of oral administration[3].
Half-life	Ibuprofen plasma half-life is between 2-8 hours. Diphenhydramine plasma half-life is between 2-4 hours.
Drug Specific Issues (if any)	None

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, fasting

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	200 mg/ 38 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None

Analytes to measure (in plasma/serum/blood):	Ibuprofen and Diphenhydramine in plasma
Bioequivalence based on:	(90% CI) Parent compound, Ibuprofen and Diphenhydramine
Waiver request of in-vivo testing:	none
Source of most recent recommendations:	Control # 06-0321 Perrigo

Summary of OGD or DBE History (for details, see Appendix 1.1):	Control Documents received: C060321 (Perrigo-03/06/06) C070908 (Dr. Reddy-06/20/07- currently open) The DBE has received the following ANDAs regarding this drug product: #90-619 (Dr. Reddy -This application), #79-113 (Perrigo), and 21-394 (Wyeth) Currently, the DBE requests the following for this drug product: 1. A single-dose fasting in-vivo bioequivalence study comparing Ibuprofen and Diphenhydramine Citrate Tablets, 200 mgl3 8 mg, to the reference listed drug (RLD), Advil PM@, (Ibuprofen and Diphenhydramine Citrate) Tablets, 200 mgl38 mg. 2. Please measure only the parent compounds, ibuprofen and diphenhydramine. 3. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following method: Apparatus: USP Apparatus I1 (paddle) Speed: 50 rpm Medium: 50 mM phosphate buffer, pH 6.5 Volume: 900 mL Sampling Times: 10, 15, 20, 30 minutes and until at leas (b)(4)% of the labeled content is dissolved.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	- -	- -
In vitro dissolution	Yes	1
Waiver requests	No	- -
BCS Waivers	- -	- -
Clinical Endpoints	- -	- -
Failed Studies	- -	- -
Amendments	Yes	2 (dissolution acknowledgement and long-term stability data)

Note[5]: Because no food effect is mentioned in the RLD labeling, only a fasting study is recommended for the drug product (see control 06-0321).

[5] Control 060321c0306

3.5 Pre-Study Bioanalytical Method Validation

A. Ibuprofen

Information Requested	Analyte 1
Bioanalytical method validation report location	Module 5.3.1.4
Analyte	Ibuprofen
Internal standard (IS)	(b) (4)
Method description	Estimation of Ibuprofen and Diphenhydramine in human plasma using API 3000 LC/MS/MS. Precipitation method (method description is detailed in method SOP attached as Appendix 1)
Limit of quantitation	500.357ng/ mL
% recovery (and %CV) at each concentration tested	83.3%
Average recovery of IS (%)	71.6%
Standard curve concentrations (units/mL)	500.357ng/ mL to 40055.904 ng/ mL
QC concentrations (units/mL)	HQC- 32051.117 ng/mL MQC- 12820.447 ng/mL LQC- 1282.045 ng/mL LOQ QC -502.562 ng/mL
QC Intraday precision range (%)	3.6– 8.3% (HQC, MQC, LQC) 3.8% (LOQ QC)
QC Intraday accuracy range (%)	102.0– 104.3% (HQC, MQC, LQC) 102.3% (LOQ QC)
QC Interday precision range (%)	4.2– 6.3% (HQC, MQC, LQC) 5.0% (LOQ QC)
QC Interday accuracy range (%)	101.7– 103.0% (HQC, MQC, LQC) 102.9% (LOQ QC)
Bench-top stability (hrs)	18 hours 39 minutes at 24±4°C
Stock stability (days)	DRUG- 07 hours at 24 ± 4°C ISTD- 07 hours at 24 ± 4°C DRUG- - 05 days 01 hours at 2 – 8°C ISTD -- 05 days 01 hours at 2 – 8°C
Processed stability (hrs)	Auto sampler- 4 days 6 hours at 10 ± 1°C Dry extract- 2 days and 22 hours at 2- 8°C Post extract – 04 hours 36 minutes at 24 ± 4°C
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	221 days
Dilution integrity (64102.234 ng/mL)	1/5th - 3.3 % (Precision), 100.4 % (Accuracy) 1/2nd –1.6 % (Precision), 100. 1% (Accuracy)
Selectivity	No significant interfering peaks were observed at the retention time of Drug and ISTD in eight (8) blank matrix lots screed

B. Diphenhydramine

Bioanalytical method validation report location	Module 5.3.1.4 (Attached as Appendix 2)		
Analyte	Diphenhydramine		
Internal standard (ISTD)	(b) (4)		
Method description	Estimation of Ibuprofen and Diphenhydramine in human plasma using API 3200 LC/MS/MS. Solid phase extraction (method description is detailed in method SOP attached as Appendix 1)		
Limit of quantification	1.015 ng/mL		
Average recovery of drug	75.1%		
Average recovery of ISTD	80.5 %		
Standard curve concentrations	1.015 to 100.640 ng/mL		
QC concentrations	HQC- 82.610 ng/mL MQC- 40.479 ng/mL LQC- 2.622 ng/mL LOQ QC – 1.023 ng/mL		
QC intra day precision range	1.9 – 4.6 % (HQC, MQC, LQC) 1.9% (LOQ QC)		
QC intra day accuracy range	99.2 – 100.4 % (HQC, MQC, LQC) 100.7 % (LOQ QC)		
QC inter day precision range	2.1 – 4.6 % (HQC, MQC, LQC) 2.8 % (LOQ QC)		
QC inter day accuracy range	99.0 – 100.1 % (HQC, MQC, LQC) 100.3 % (LOQ QC)		
Bench-top stability	08 hours 03 minutes at 24±4°C		
Stock solution stability	Short Term	Drug	10 Hours 16 Minutes at 24 ± 4°C
		ISTD	10 Hours 16 Minutes at 24 ± 4°C
	Long Term	Drug	4 days 01 hour at 2 – 8°C
		ISTD	4 days 01 hour at 2 – 8°C
Processed Stability	Auto sampler- 28 hours 42 minutes at 15 ± 5°C Dry extract- 23 hours 11 minutes at 2- 8°C Post extract – 5 hours at 24±4°C		
Freeze-thaw stability	3 cycles		
Long-term storage stability (days)	216 days		
Dilution integrity (161.024 ng/mL)	1/5th –3.2% (Precision), 95.6% (Accuracy) 1/2nd –1.4% (Precision), 98.5% (Accuracy)		
Selectivity	No significant interfering peaks were observed at the retention time of Drug and ISTD in eight (8) blank matrix lots screed		

Note: After reviewing the data of subject 01, 02 it was observed that C_{max} of Diphenhydramine was about 20 ng/ mL and was about 5 ng/mL for Nor-diphenhydramine. So it was decided to change the linearity range from 1.018 – 99.680 ng/mL to 1.000 - 50.000 ng/mL for Diphenhydramine and 1.030 - 100.873 ng/mL to 1.000 – 15.000ng/ mL for Nor-diphenhydramine. Bulk spiking was performed again and with above mentioned linearity and subject 01, 02 were repeated.

SOPs submitted	Yes
Bioanalytical method is acceptable	Acceptable

Comments on the Pre-Study Method Validation:

1. The frozen, long-term stability data of 221 days for ibuprofen and 216 days for diphenhydramine exceed the storage period for both the fasted (36 days for ibuprofen and 43 days for diphenhydramine) and fed (48 days for ibuprofen and 50 days for diphenhydramine) BE studies.

2. The firm used K_2EDTA as anticoagulant for the method validation and clinical studies.

3. The pre-study method validation is acceptable. The firm's report describes the validated bioanalytical method "Estimation of Ibuprofen in presence of Diphenhydramine and Nor-Diphenhydramine in human plasma using LCIMSIMS" and "Estimation of Diphenhydramine and Nor-Diphenhydramine in presence of Ibuprofen in human plasma using LC/MSIMS" for determining concentration of Ibuprofen, Diphenhydramine and Nor-Diphenhydramine in human plasma.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

A. Ibuprofen

Study Ref. No.	Study Objective	Study design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subject No. (M/F) Type Age: mean (Range)	Parameters						Study Report Location
					C_{max} (ng/mL) Mean ± SD (CV %)	t_{max} (hr) Median (Range)	AUC_{0-T} (ng hr/mL) Mean ± SD (CV %)	AUC_{0-INF} (ng hr/mL) Mean ± SD (CV %)	$t_{½}$ (hr) Mean ± SD (CV %)	K_{el} (hr^{-1}) Mean ± SD (CV %)	
149-07	Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study of Ibuprofen + Diphenhydramine citrate 200 mg/38 mg caplets of Dr. Reddy's Laboratories Limited, India and Advil®PM, of Wyeth Consumer Healthcare, USA., in normal, healthy, adult, human subjects under fasting conditions.	A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study in normal, healthy, adult, human subjects under fasting conditions.	**Test product (T)** IBUPROFEN AND DIPHENHYDRAMINE CITRATE CAPLETS 200 mg/38 mg, Dr. Reddy's Laboratories Limited, India Batch No.: EC8063 Mfg Date: FEB. 2008 Exp Date: NAV Route of administration: Oral	Forty (40) normal, healthy, adult male subjects were enrolled in the study and all the subjects completed the study. (N=40, mean Age=24.6 Range=18-40)	19622.1510 ± 3150.5089 (16.1)	2.330 (0.75-4.00)	69248.5898 ± 12137.5017 (17.5)	71639.6262 ± 13070.1643 (18.2)	1.9732 ± 0.4237 (21.5)	0.3666 ± 0.0759 (20.7)	Page No. 61 of 283
			Reference product (R) Advil®PM (Ibuprofen, 200mg/Diphenhydramine citrate, 38 mg caplets Wyeth consumer health care, USA. Lot No.: B65608 Mfg Date: NAV Exp Date: Apr 2009 Route of administration: Oral		18915.2510 ± 3546.3071 (18.7)	2.330 (0.75-4.00)	68927.7656 ± 10998.7058 (16.0)	71299.2933 ± 11625.9170 (16.3)	1.9335 ± 0.3211 (16.6)	0.3680 ± 0.0602 (16.4)	

B. Diphenhydramine

Study Ref. No.	Study Objective	Study design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subject No. (M/F) Type Age: mean (Range)	Parameters						Study Report Location
					C_{max} (ng/mL) Mean ± SD (CV %)	t_{max} (hr) Median (Range)	AUC_{0-T} (ng.hr/mL) Mean ± SD (CV %)	AUC_{0-INF} (ng.hr/mL) Mean ± SD (CV %)	$t_{½}$ (hr) Mean ± SD (CV %)	K_{el} (hr^{-1}) Mean ± SD (CV %)	
149-07	To determine the single-dose oral bioequivalence of Ibuprofen and Diphenhydramine citrate caplets 200 mg/38 mg, Dr. Reddy's Laboratories Limited, India and Advil®PM (Ibuprofen, 200 mg Diphenhydramine citrate, 38 mg caplets) Wyeth consumer health care, USA in normal, healthy, adult, human subjects under fasting conditions	A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study in normal, healthy, adult, human subjects under fasting conditions.	**Test product (T)** IBUPROFEN AND DIPHENHYDRAMINE CITRATE CAPLETS 200 mg/38 mg, Dr. Reddy's Laboratories Limited, India Batch No.: EC8063 Mfg Date: FEB. 2008 Exp Date: NAV Route of administration: Oral	Forty (40) normal, healthy, adult male subjects were enrolled in the study and all the subjects completed the study. (N=40, mean Age=24.6 Range=18-40)	33.8909 ± 10.3968 (30.7%)	2.670 (1.00 - 5.00)	324.7345 ± 113.1403 (34.8)	353.2940 ± 116.9970 (33.1)	9.0047 ± 1.5508 (17.2)	0.0794 ± 0.0152 (19.1)	Page No. 62 of 283
			Reference product (R) Advil®PM (Ibuprofen, 200mg/Diphenhydramine citrate, 38 mg caplets Wyeth consumer health care, USA. Lot No.: B65608 Mfg Date: NAV Exp Date: Apr 2009 Route of administration: Oral		33.9382 ± 9.1921 (27.1)	2.670 (1.00-6.00)	325.3947 ± 116.3460 (35.8)	352.0347 ± 124.6016 (35.4)	8.6113 ± 1.8588 (21.6)	0.0846 ± 0.0208 (24.6)	

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

A. Ibuprofen

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (149-07)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	68235.31	68066.99	1.00	98.01	102.54
AUC∞ (ng·hr/mL)	70526.44	70377.91	1.00	97.98	102.50
Cmax (ng/mL)	19353.31	18587.17	1.04	98.65	109.89

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (155-07)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	68165.01	66501.71	1.03	98.84	106.29
AUC∞ (ng·hr/mL)	71608.68	69166.27	1.04	99.82	107.38
Cmax (ng/mL)	15700.17	16347.86	0.96	90.37	102.06

B. Diphenhydramine

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (149-07)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	306.84	304.96	1.01	94.75	106.84
AUC∞ (ng·hr/mL)	335.87	331.44	1.01	95.99	106.99
Cmax (ng/mL)	32.34	32.69	0.99	93.81	104.34

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (155-07)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	354.90	369.70	0.96	90.52	101.80
AUC∞ (ng·hr/mL)	381.69	401.79	0.95	89.84	100.45
Cmax (ng/mL)	38.56	40.10	0.96	89.02	103.86

Table 3. Reanalysis of Study Samples

A. Ibuprofen

Fasting Bioequivalence Study (Study No. 149-07) Additional information in Volume(s), Page(s)								
Repeat Code	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual No.		**% of total assays**		**Actual No.**		**% of total assays**	
	Test	**Reference**	**Test**	**Reference**	**Test**	**Reference**	**Test**	**Reference**
Pharmacokinetic	0	0	0.0	0.00	0	0	0.0	0.00
D- Improper sample processing	1	3	0.1	0.2	1	3	0.1	0.2
F - Poor Chromatography	17	8	1.0	0.5	17	8	1.0	0.5
Total	18	11	1.1	0.7	18	11	1.1	0.7
Total No. of samples analyzed: 1680								

Fed Bioequivalence Study (Study No. 155-07) Additional information in Volume(s), Page(s)								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.0	0.0	0	0	0.0	0.0
Improper sample processing	3	0	0.2	0.0	3	0	0.2	0.0
Response in pre-dose sample	0	1	0.0	0.1	0	1	0.0	0.1
Poor chromatography	4	5	0.2	0.3	4	5	0.2	0.3
Total	7	6	0.4	0.4	7	6	0.4	0.4
Total number of	1919							

samples analyzed	

B. Diphenhydramine

Fasting Bioequivalence Study (Study No. 149-07) Additional information in Volume(s), Page(s)								
Repeat Code	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual No.		% of total assays		Actual No.		% of total assays	
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Pharmacokinetic	0	0	0.0	0.00	0	0	0.0	0.00
B-Value above upper limit of CC	8	6	0.5	0.4	8	6	0.5	0.4
C- Aberrant value	0	4	0.0	0.2	0	4	0.0	0.2
D- Improper sample processing	0	1	0.0	0.1	0	1	0.0	0.1
Total	8	11	0.5	0.7	8	11	0.5	0.7
Total No. of samples analyzed: 1680								

Fed Bioequivalence Study (Study No. 155-07) Additional information in Volume(s), Page(s)								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.0	0.0	0	0	0.0	0.0
B- Value above upper limit of CC	40	28	2.1	1.5	40	28	2.1	1.5
C- Aberrant value	4	1	0.2	0.1	0	1	0.0	0.1
D-Improper sample processing	4	4	0.2	0.2	4	4	0.2	0.2
*	1	1	0.1	0.1	1	1	0.1	0.1
Total	49	34	2.6	1.9	45	34	2.4	1.9
Total number of samples analyzed	1919							

*-Vial interchange (SOP Deviation)

Did use of recalculated plasma concentration data change study outcome? No

Comments from the Reviewer:

1. There were no pharmacokinetic repeats for Ibuprofen or Diphenhydramine in the fasting study (149-07). The other repeat assays were conducted objectively based on BR030_04. Also, the reviewer reanalyzed the data using the original values available and the 90% confidence intervals still remained within the acceptable range.

2. There were no pharmacokinetic repeats for Ibuprofen or Diphenhydramine in the fed study (155-07). The other repeat assay was conducted objectively based on BR030_04. Also, the reviewer reanalyzed the data using the original values available and the 90% confidence intervals still remained within the acceptable range.

3.7 Formulation

Location in appendix	Section 4.2, Page 53
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**ACCEPTABLE**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DFS: N 090619 N 000 13-Jun-2008
Source of Method (USP, FDA or Firm)	FDA-recommended method
Medium	50 mM Phosphate buffer, pH 6.5
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
DBE-recommended specifications	NLT (b)(4)% (Q) in 30 minutes for ibuprofen and diphenhydramine
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	N/A
If no, reason why F2 not calculated	Rapidly dissolving
Is method acceptable?	METHOD ACCEPTABLE
If not then why?	N/A

3.9 Waiver Request(s)

None

3.10 Deficiency Comments

1. The firm has submitted two (2) different sets of 90% CI data for **diphenhydramine** in the fed study (155-07). The 90% CI values submitted in the firm's **Table 3**: Statistical Summary of the Comparative Bioavailability Data of 155-07 (Fed study) were inconsistent with the 90% CI data submitted in the study report (page 484), which is the firm's statistical analysis of diphenhydramine in the fed study. The firm should explain this discrepancy.

Table 3: Statistical Summary of the Comparative Bioavailability Data of 155-07 (Fed study)

Ibuprofen + Diphenhydramine citrate 200 mg/38 mg caplets Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study No. 155-07)				
Diphenhydramine				
AUC_{0-INF} (ng*h/mL)	381.6884	401.7938	95.00	89.84 - 100.45
AUC_{0-t} (ng*hr/mL)	354.9011	369.7046	96.00	98.84 - 106.29
C_{max} (ng/mL)	38.5564	40.0983	96.15	90.37 - 102.06

Project No.:155-07 15:07 Monday, May 26, 2008

Statistical Analysis for log transformed PK Parameters of Diphenhydramine

Pkpar	ISCV	lsm_T	lsm_R	Ratio	LCL	UCL	BIOEQUIVALENCE	Power
LnCmax	20.7	38.5564	40.0983	96.15	89.02	103.86	YES	99.9
LnAUC0-T	15.7	354.9011	369.7046	96.00	90.52	101.80	YES	100.0
LnAUC0-INF	14.9	381.6884	401.7938	95.00	89.84	100.45	YES	100.0

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (149-07) acceptable. Dr. Reddy, conducted the fasting BE study on its test product, Ibuprofen / Diphenhydramine Caplet, 200 mg/ 38 mg , (lot # EC8063) comparing it to Wyeth's Advil PM® Caplet, 200 mg/ 38 mg (lot # B65608).

2. The Division of Bioequivalence finds the fed BE study (155-07) incomplete. Dr. Reddy conducted the fed BE study on its test product, Ibuprofen/ Diphenhydramine Caplet, 200 mg/ 38 mg, (lot # EC8063) comparing it to Wyeth's Advil PM® Caplet, 200 mg/ 38 mg (lot # B65608).

3. The firm's *in vitro* dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 50 mM Phosphate buffer, pH 6.5 at 37ºC $\pm$ 0.5ºC using USP

apparatus 2 (paddle) at 50 rpm. The test product should meet the following specification(s): NLT (b) (4)% (Q) of both drug components in the dosage form is dissolved in 30 minutes.

4. This application is **incomplete.**

The firm should be informed of the above deficiency comment and recommendations.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
None	- -

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	149-07
Study Title	Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study of Ibuprofen + Diphenhydramine citrate 200 mg/38 mg Caplets of Dr. Reddy's Laboratories Limited, India and Advil®PM, of Wyeth consumer health care, USA in normal, healthy, adult, human subjects under fasting conditions.
Clinical Site (Name & Address)	GVK BIOSCIENCES PVT LTD., Clinical Pharmacology Unit 7th Floor, Swarna Jayanthi Commercial Complex Ameerpet, Hyderabad – 500 038. Phone: +91-40-6662 8888; 6627 5555 Fax: +91-40-6627 5599
Principal Investigator	Dr. N.Netaji, MD
Dosing Dates	Period 01: 04 Apr 2008 Period 02: 11 Apr 2008
Analytical Site (Name & Address)	(b) (4)

	Fax: +91-40-6627 5599
Analysis Dates	22 Feb 2008 – 29 Feb 2008
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	Ibuprofen: 36 Diphenhydramine and Nor-Diphenhydramine: 43

Table 5. Product information

Product	Test	Reference
Treatment ID	T	R
Product Name	Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg.	Advil ® PM Caplets (Ibuprofen, 200mg and Diphenhydramine Citrate, 38 mg Caplets)
Manufacturer	Dr. Reddy's Laboratories Limited, Bachepalli – 502 325, INDIA	Wyeth Consumer Healthcare, USA
Batch/Lot No.	EC8063	B65608
Manufacture Date	February 2008	N/A
Expiration Date	N/A	April 2009
Strength	200 mg/38 mg	200 mg/38 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	For Ibuprofen (b) (4)%	For Ibuprofen: (b) (4)%
	For Diphenhydramine (b) (4)%	For Diphenhydramine: (b) (4)%
Content Uniformity (Mean, %CV)	For Ibuprofen: Mean: 101%, %CV: 1.1	N/A
	For Diphenhydramine: Mean: 99.7%, %CV: 1.1	
Dose Administered	200 mg/38 mg	200 mg/38 mg
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	40 subjects enrolled and dosed in the study 40 subjects completed the study (dropouts: none) 40 subjects included in the statistical analysis
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1 group
Washout Period	At least 7 days

Randomization Scheme	AB: 1, 3, 5, 7, 9, 12, 14, 15, 18, 20, 22, 23, 26, 28, 30, 32, 34, 35, 37 and 40 BA: 2, 4, 6, 8, 10, 11, 13, 16, 17, 19, 21, 24, 25, 27, 29, 31, 33, 36, 38 and 39
Blood Sampling Times	Pre-dose (0), 0.25, 0.5, 0.75, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 24.00 and 36.00 hours post-dose
Blood Volume Collected/Sample	Twenty one samples were collected from each subject during each period. The venous blood samples (6 mL each) were withdrawn at the sample times listed above. Blood samples were collected through an indwelling cannula placed in forearm vein using disposable syringe or through fresh venipuncture with disposable syringes and needles. Heparin-lock technique (about 1 mL of 5 IU/mL heparin **in** normal saline solution was injected into the cannula after each sample collection) was used to prevent clotting of the blood **in** the indwelling cannula. While sampling through the cannula, blood samples were collected after discarding the first 0.5 mL of heparinised blood from the tubing of the cannula except for predose and ambulatory sample.
Blood Sample Processing/Storage	At each time point, the blood samples were collected **in** pre-labeled (Project No., Subject No., Period, Sampling time point and Sample ID) vacuettes®/vacutainers® containing K2EDTA as anticoagulant. After collecting the blood samples from all the subjects at each sampling time point, samples were centrifuged under refrigeration with machine set at 3000 rpm, 10 minutes and 4°C. After centrifugation the plasma samples were separated and transferred into respective prelabeled polypropylene tubes in duplicate (set # 01 & set # 02). These polypropylene tubes were stored below -20°C for a maximum period of 12 hours and then they were stored at -70°C ± 20°C until withdrawn for analysis. In case meal and blood sample collection timings coincide, samples were collected before meals were provided. Sample collection and processing was done under minimal exposure to ultraviolet light.
IRB Approval	Yes, April 1, 2008
Informed Consent	Yes, April 1, 2008
Length of Fasting	An overnight fast of at least 10.5 hours prior to dose administration after which a fast (except water) was maintained until at least 4 hours after dosing.
Length of Confinement	For at least 10.5 hours prior to drug administration until 24 hours post dose. Volunteers returned to the clinical site for the 24 hour and 36 hour blood sample.
Safety Monitoring	Clinical Examination was carried out and recorded at check-in and at checkout in each period. Vital signs (seated blood pressure, radial pulse rate, respiratory rate and axillary temperature) were measured and recorded at check in, before dosing of investigational products (in the morning of the day of dosing) and at check out. Vital signs (seated blood pressure and radial pulse rate) were measured and recorded 1, 2, 3, 4 and 12 hours after dosing, within ± 30 minutes of scheduled time.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. 149-07			
		Treatment Groups	
		Test Product N = 40	Reference Product N = 40
Age (years)	Mean ± SD	24.6 ± 6.61	24.6 ± 6.61
	Range	18-40	18-40
Age Groups	< 18	0	0
	18 – 40	40 (100%)	40 (100%)
	41 – 64	0	0
	65 – 75	0	0
	> 75	0	0
Sex	Male	0	0
	Female	40 (100%)	40 (100%)
Race	Asian	40 (100%)	40 (100%)
	Black	0	0
	Caucasian	0	0
	Hispanic	0	0
	Other	0	0
BMI	Mean + SD	21.07 ± 2.178	21.07 ± 2.178
	Range	18.7-24.9	18.7-24.9
Other Factors		Nil	Nil

Table 8. Dropout Information, Fasting Bioequivalence Study

None

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body system/adverse event	Reported incidence by treatment groups		
	Fasting Bioequivalence study 149-07 (N= 40)		
	Test	Reference	Post Study Safety
Investigations			
Elevated eosinophils	-	-	5 (12.5%)
Elevated serum triglycerides	-	-	4 (10%)
Elevated total bilirubin	-	-	1 (2.5%)
Decreased lymphocytes	-	-	1 (2.5%)
Decreased total WBC Count	-	-	1 (2.5%)
Nervous system disorders			
Dizziness	-	1 (2.5%)	-
Total	-	1 (2.5%)	12 (30%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Inclusion/Exclusion criteria	-	-
Sampling Time Point Protocol Deviations Period 01	18	12
Sampling Time Point Protocol Deviations Period 02	-	-

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. No serious adverse events (SAEs) were reported during the fasting BE study.

2. Subjects that experienced an adverse event did not require the use of concomitant medications during the course of this study.

3. Two blood sampling deviations were recorded. The actual sampling times were used in the pharmacokinetic calculations. The blood sampling time deviations were insignificant.

4. No subject experienced emesis during the fasting study.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

A. Ibuprofen

Fasting Bioequivalence Study (Study No. 149-07) Analyte Name: Ibuprofen								
Parameter	**Standard Curve Samples**							
ID of STD	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Concentration (ng/mL)	40047.730	34441.048	26691.812	18150.432	9982.738	3993.095	1078.136	500.471
Inter day Precision (% CV)	3.9	2.8	3.5	3.8	4.5	5.1	3.8	1.6
Inter day Accuracy (%Accuracy)	95.8	93.5	98.9	101.5	105.0	108.3	98.5	99.6
r^2 range	0.9884 – 0.9990							
Linearity range (ng/mL)	500.471 - 40047.730							
Sensitivity (ng/mL)	500.471							

Fasting Bioequivalence Study (Study No. 149-07) Analyte Name: Ibuprofen			
Parameter	**Quality Control Samples**		
QC ID	HQC	MQC	LQC
Concentration (ng/mL)	32052.291	12820.916	1282.092
Inter day precision (%CV)	5.2	6.9	5.6
Inter day accuracy (% Accuracy)	101.7	103.2	101.0

B. Diphenhydramine

	Fasting Bioequivalence Study (Study No. 149-07) Analyte Name: Diphenhydramine							
Parameter	Calibration Curve Standards							
ID of STD	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Concentration (ng/ mL)	50.344	43.296	32.472	22.730	13.638	5.455	2.564	1.051
Inter day Precision (% CV)	2.8	4.1	4.3	2.8	3.6	3.8	5.2	1.8
Inter day Accuracy (%Accuracy)	98.8	97.4	98.8	101.4	99.7	104.5	100.4	99.1
r^2 range	0.9922 – 0.9999							
Linearity range (ng/ mL)	1.051 - 50.344							
Sensitivity (ng/ mL)	1.051							

Fasting Bioequivalence Study (Study No. 149-07) Analyte Name: Diphenhydramine				
Parameter	**Quality Control Samples**			
QC ID	HQC	MQC	M2QC	LQC
Concentration (ng/ mL)	40.222	18.100	9.050	2.643
Inter day precision (%CV)	5.2	5.2	5.0	5.4
Inter day accuracy (% Accuracy)	104.5	101.7	102.1	102.1

Comments on Study Assay Validation:

Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially (Subjects #5, #6, #7, #8, #9, #10, #11, #12, #13 and #14)

Comments on Chromatograms:

Acceptable

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
BR030_04	27 Oct 2006	Repeat Analysis

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Agree
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

Acceptable

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 19 and Figure 2

A. Ibuprofen

Fasting Bioequivalence Study, Study No. 149-07									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	69248.59	17.53	48421.67	99383.97	68927.77	15.96	46925.98	94499.39	1.00
AUC∞ (hr *ng/ml)	71639.63	18.24	49985.44	106785.1	71299.29	16.31	48321.98	100453.1	1.00
Cmax (ng/ml)	19622.15	16.06	10494.95	24984.55	18915.25	18.75	12584.68	25929.80	1.04
Tmax* (hr)	2.33	.	0.75	4.00	2.33	.	0.75	4.00	1.00
Kel (hr^{-1})	0.37	20.71	0.23	0.55	0.37	16.37	0.25	0.55	1.00
T1/2 (hr)	1.97	21.47	1.26	3.02	1.93	16.60	1.27	2.77	1.02

* Tmax values are presented as median, range

B. Diphenhydramine

Fasting Bioequivalence Study, Study No. 149-07									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	324.73	34.84	120.62	739.77	325.39	35.76	103.97	667.34	1.00
AUC∞ (hr *ng/ml)	353.29	33.12	134.09	793.70	352.03	35.39	131.91	732.40	1.00
Cmax (ng/ml)	33.89	30.68	16.54	58.07	33.94	27.08	13.64	54.88	1.00
Tmax* (hr)	2.67	.	1.00	5.00	2.67	.	1.00	6.00	1.00
Kel (hr^{-1})	0.08	19.07	0.06	0.13	0.08	24.64	0.05	0.15	0.94
T1/2 (hr)	9.00	17.22	5.30	12.47	8.61	21.59	4.49	13.48	1.05

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

A. Ibuprofen

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 149-07				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (ng·hr/mL)	68235.3129	68066.9945	100.25	98.01 - 102.54
AUC∞ (ng·hr/mL)	70526.4449	70377.9070	100.21	97.98 - 102.50
Cmax (ng/mL)	19353.3113	18587.1731	104.12	98.65 - 109.89

B. Diphenhydramine

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 149-07				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (ng·hr/mL)	306.8366	304.9641	100.61	94.75 - 106.84
AUC∞ (ng·hr/mL)	335.8696	331.4388	101.34	95.99 - 106.99
Cmax (ng/mL)	32.3377	32.6864	98.93	93.81 - 104.34

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

A. Ibuprofen

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 149-07					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	68235.31	68066.99	1.00	98.01	102.54
AUC∞ (ng·hr/mL)	70526.44	70377.91	1.00	97.98	102.50
Cmax (ng/mL)	19353.31	18587.17	1.04	98.65	109.89

B. Diphenhydramine

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 149-07					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	306.84	304.96	1.01	94.75	106.84
AUC∞ (ng·hr/mL)	335.87	331.44	1.01	95.99	106.99
Cmax (ng/mL)	32.34	32.69	0.99	93.81	104.34

Table 17. Additional Study Information, Fasting Study No. 149-07

Root mean square error, AUC0-t	0.0600 Ibuprofen 0.1593 Diphenhydramine	
Root mean square error, AUC∞	0.0598 Ibuprofen 0.1439 Diphenhydramine	
Root mean square error, Cmax	0.1431 Ibuprofen 0.1410 Diphenhydramine	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	40	40
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞					
Treatment		**n**	**Mean**	**Minimum**	**Maximum**
Test	Ibuprofen	40	0.97	0.91	0.98
	Diphenhydramine	40	0.91	0.81	0.97
Reference	Ibuprofen	40	0.97	0.94	0.98
	Diphenhydramine	40	0.92	0.79	0.97

Comments on Pharmacokinetic and Statistical Analysis:

The mean AUCt/AUC∞ ratio >0.9 for both test and reference indicates that the firm's sampling schedule was carried out for a sufficient period of time. All subjects illustrated an AUCt/AUC∞ ratio >0.79 for ibuprofen and diphenhydramine. The SAS program CONTINU was used to verify the firm's data.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The single-dose fasting bioequivalence study on 1 x 200 mg/ 38 mg caplet is acceptable.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Analyte 1 (Ibuprofen)					
Time (hr)	Test (n= 40)		Reference (n= 40)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.25	2646.04	113.78	1990.26	131.85	1.33
0.50	5777.70	90.58	5304.09	88.43	1.09
0.75	7287.28	85.85	7663.79	82.57	0.95
1.00	8300.84	71.75	8955.01	76.51	0.93
1.33	10086.17	63.69	10502.89	63.05	0.96
1.67	12055.81	47.78	12071.80	47.77	1.00
2.00	13238.44	37.76	13375.14	41.61	0.99
2.33	14060.89	38.44	14013.44	35.28	1.00
2.67	13731.05	32.82	14309.28	28.78	0.96
3.00	12986.81	33.85	13449.46	28.53	0.97
3.33	12618.36	35.89	12887.18	29.50	0.98
3.67	11943.76	33.77	11999.85	30.00	1.00
4.00	11590.78	38.71	11041.22	32.23	1.05
5.00	7422.91	37.32	7296.02	36.65	1.02
6.00	4753.28	41.89	4606.92	36.62	1.03
8.00	2298.25	44.40	2242.26	44.44	1.02
10.00	1137.37	55.45	1103.45	56.56	1.03
12.00	485.10	103.22	472.42	103.22	1.03
24.00	0.00	.	0.00	.	.
36.00	0.00	.	0.00	.	.

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

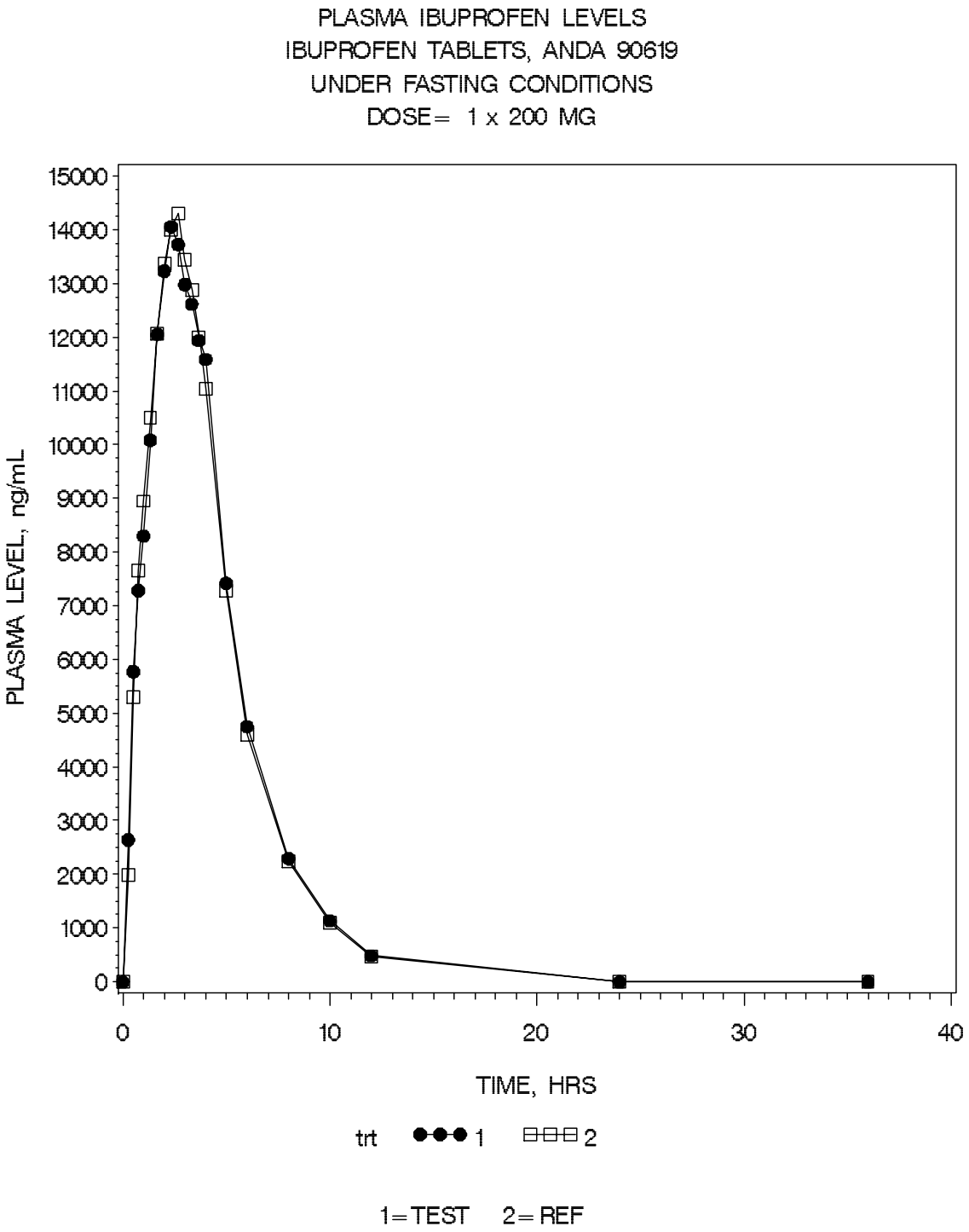
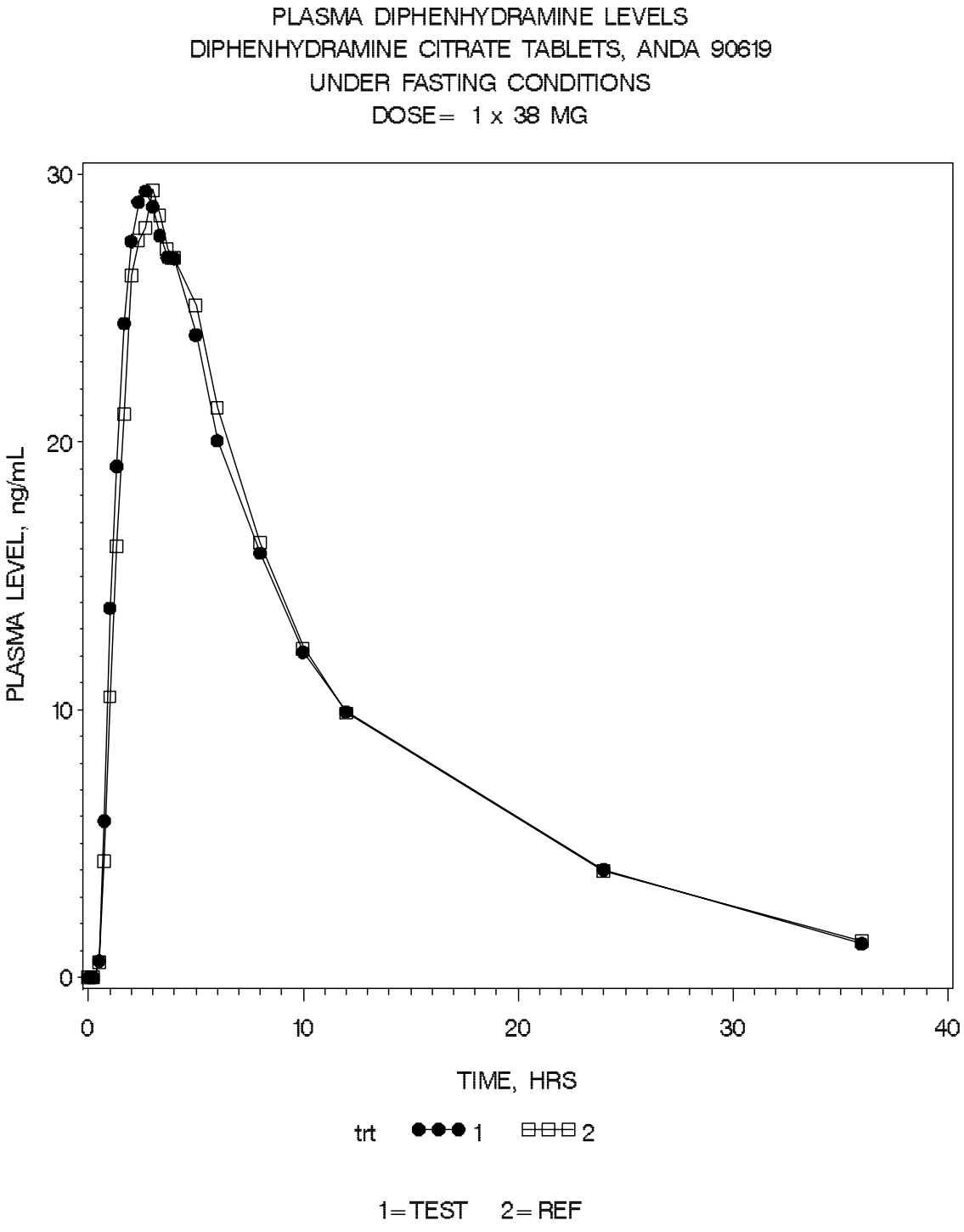


Table 19. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Analyte 1 (Diphenhydramine)					
Time (hr)	Test (n= 40)		Reference (n= 40)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.25	0.00	.	0.00	.	.
0.50	0.61	175.34	0.56	236.94	1.09
0.75	5.85	92.01	4.36	127.80	1.34
1.00	13.80	74.01	10.49	93.51	1.31
1.33	19.10	46.99	16.12	66.85	1.18
1.67	24.44	43.46	21.06	51.28	1.16
2.00	27.51	37.28	26.23	43.35	1.05
2.33	28.98	38.62	27.55	36.26	1.05
2.67	29.39	31.98	28.02	32.20	1.05
3.00	28.80	27.53	29.43	28.02	0.98
3.33	27.72	29.67	28.49	31.61	0.97
3.67	26.91	28.90	27.20	32.04	0.99
4.00	26.86	28.44	26.90	29.68	1.00
5.00	24.01	32.35	25.11	32.19	0.96
6.00	20.06	33.96	21.29	32.74	0.94
8.00	15.86	38.80	16.25	31.64	0.98
10.00	12.16	39.24	12.30	37.50	0.99
12.00	9.93	41.48	9.88	39.25	1.00
24.00	4.03	43.47	3.97	51.57	1.01
36.00	1.26	87.45	1.35	84.74	0.93

Figure 2. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 20. Study Information

Study Number	155-07
Study Title	Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study of Ibuprofen + Diphenhydramine citrate 200 mg/38 mg caplets of Dr. Reddy's Laboratories Limited, India and Advil®PM, of Wyeth consumer health care, USA in normal, healthy, adult, human subjects under fed conditions.
Clinical Site (Name & Address)	GVK Biosciences Pvt. Ltd. Clinical Pharmacology Unit 7th Floor, Swarna Jayanthi Commercial Complex, Ameerpet, Hyderabad – 500 038, India.
Principal Investigator	Dr. N.Netaji
Dosing Dates	Period 01: 04 Apr 2008 Period 02: 11 Apr 2008
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	Ibuprofen: 12 May 2008 to 21 May 2008 Diphenhydramine and Nor-Diphenhydramine: 10 may 2008 to 23 May 2008
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	Ibuprofen: 48 Days Diphenhydramine and Nor-Diphenhydramine: 50 Days

Table 21. Product Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg.	Advil ® PM Caplets (Ibuprofen, 200mg and Diphenhydramine Citrate, 38 mg Caplets)
Manufacturer	Dr. Reddy's Laboratories Limited, Bachepalli – 502 325, INDIA	Wyeth Consumer Healthcare, USA
Batch/Lot No.	EC8063	B65608
Manufacture Date	February 2008	N/A
Expiration Date	N/A	April 2009
Strength	200 mg/38 mg	200 mg/38 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	For Ibuprofen: (b) (4)%	For Ibuprofen: (b) (4)%
	For Diphenhydramine (b) (4)%	For Diphenhydramine: (b) (4)%
Content Uniformity (Mean, %CV)	For Ibuprofen: Mean: 101%, %CV: 1.1	N/A
	For Diphenhydramine: Mean: 99.7%, %CV: 1.1	
Dose Administered	200 mg/38 mg	200 mg/38 mg
Route of Administration	Oral	Oral

Table 22. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	40 subjects enrolled and dosed in the study 40 subjects completed the study (dropouts: none) 40 subjects included in the statistical analysis
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1 group
Washout Period	At least 7 days
Randomization Scheme	AB: 1, 3, 5, 8, 9, 11, 14, 16, 17, 20, 21, 23, 25, 28, 29, 32, 33, 36, 38 and 39 BA: 2, 4, 6, 7, 8, 10, 11, 12, 13, 15, 18, 19, 21, 24, 26, 27, 30, 31, 34, 35 37 and 40
Blood Sampling Times	Pre-dose (0), 0.25, 0.5, 0.75, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 24.00 and 36.00 hours post-dose
Blood Volume Collected/Sample	Twenty four samples were collected from each subject during each period. The venous blood samples (6 mL each) were withdrawn at the sample times listed above. Blood samples were collected through an indwelling cannula placed in forearm vein using disposable syringe or through fresh venipuncture with disposable syringes and needles. Heparin-lock technique (about 1 mL of 5 IU/mL heparin in normal saline solution was injected into the cannula after each sample collection) was used to prevent clotting of the blood in the indwelling cannula. While sampling through the cannula, blood samples were collected after discarding the first 0.5 mL of heparinised blood from the tubing of the cannula except for predose and ambulatory sample
Blood Sample Processing/Storage	At each time point, the blood samples were collected in pre-labeled (Project No., Subject No., Period, Sampling time point and Sample ID) vacutainers containing K2EDTA as anticoagulant. After collecting the blood samples from all the subjects at each sampling time point, samples were centrifuged under refrigeration with machine set at 3000 rpm, 10 minutes and 4°C. After centrifugation the plasma samples were separated and transferred into respective prelabeled polypropylene tubes in duplicate (set # 01 & set # 02). These polypropylene tubes were stored below -20°C for a maximum period of 12 hours and then they were stored at 70° C ± 20°C until withdrawn for analysis.
IRB Approval	Yes, April 1, 2008
Informed Consent	Yes, April 1, 2008

Length of Fasting Before Meal	Subjects were fasted overnight for at least 10 hours prior to scheduled time for a high fat breakfast (about 1000 cal); dosing was done 30 minutes after the start of the breakfast. Lunch was served 4 hours after dosing.
Length of Confinement	For at least 10.5 hours prior to drug administration until 24 hours post dose. Volunteers returned to the clinical site for the 24 hour and 36 hour blood sample.
Safety Monitoring	Clinical Examination was carried out and recorded at check-in and at checkout in each period. Vital signs (seated blood pressure, radial pulse rate, respiratory rate and axillary temperature) were measured and recorded at check in, before dosing of investigational products (in the morning of the day of dosing) and at check out. Vital signs (seated blood pressure and radial pulse rate) were measured and recorded 1, 2, 3, 4 and 12 hours after dosing, within ± 30 minutes of scheduled time.

Standard FDA Meal Used?	No	
If No, then meal components and composition is listed in the tables below		
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**
Fat	55.45	541.44
Carbohydrate	28.60	279.28
Protein	15.95	155.72
Total	100.00	976.44

Components of Non-standard FDA Meal Used in Fed Bioequivalence Study

Meal ID: 155/02		Meal Type: Fed breakfast			
S.No	Food Item	Portion Size (Cooked weight)			
1	Toast with butter	2 no.			
2	Fried chicken	¼ cup			
3	Egg (Fried in Butter)	2 no.			
4	French Fries	1 cup			
5	Milk	1 glass			
Nutritive value of food items (Raw weight)					
S.No	Food item	Quantity (gm)/(ml)	Protein (Gram)	Fat (Gram)	Carbohydrates (Gram)
1	Wheat refined	40	3.10	0.40	20.70
2	Chicken	50	12.95	0.30	0
3	Egg	80	10.64	10.64	0
4	Potato	120	1.92	0.12	27.12
5	Milk (Whole milk)	240	10.32	15.60	12.00
6	Sugar	10	0	0	10.00
7	Oil	25	0	25.00	0
8	Butter	10	0	8.10	0
Total			38.93	60.16	69.82
Energy (Kcal)			155.72	541.44	279.28
Total Energy (Kcal)			976.44		
Percentage of Caloric Content			15.95	55.45	28.60

Note: Portion size of food item may vary depending on the amount of water added during cooking

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 23. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No.			
		Treatment Groups	
		Test Product N = 40	Reference Product N = 40
Age (years)	Mean ± SD	25.5 ± 5.36	25.5 ± 5.36
	Range	19 - 41	19 - 41
Age Groups	< 18	0	0
	18 – 40	39 (97.5%)	39 (97.5%)
	41 – 64	1 (2.5%)	1 (2.5%)
	65 – 75	0	0
	> 75	0	0
Sex	Male	40(100%)	40(100%)
	Female	0	0
Race	Asian	40 (100%)	40 (100%)
	Black	0	0
	Caucasian	0	0
	Hispanic	0	0
	Other	0	0
BMI	Mean + SD	21.34 ± 1.795	21.34 ± 1.795
	Range	18.5 - 24.7	18.5 - 24.7
Other Factors		Nil	Nil

Table 24. Dropout Information, Fed Bioequivalence Study

None

Table 25. Study Adverse Events, Fed Bioequivalence Study

Body system/adverse event	Reported Incidence by Treatment Groups		
	Fed Bioequivalence Study Study No. 155-07		
	Test	Reference	Post Study Safety
Nervous system disorders			
Dizziness	1 (2.5%)	-	-
Investigations			
Elevated serum amylase	-	-	1 (2.5%)
Elevated eosinophils	-	-	5 (12.5%)
Elevated total bilirubin	-	-	1 (2.5%)
Elevated total WBC count	-	-	2 (5.0%)
Decreased lymphocytes	-	-	2 (5.0%)
Elevated serum triglycerides	-	-	5 (12.5%)
Elevated lymphocytes	-	-	1 (2.5%)
Elevated ALP	-	-	1 (2.5%)
Total	**1 (2.5%)**	**-**	**18 (45%)**

Table 26. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Inclusion/Exclusion criteria	-	-
Sampling Time Point Protocol Deviations	09	06

Comments on Adverse Events/Protocol Deviations:

1. No serious adverse events (SAEs) were reported during the fed BE study.
2. Two blood sampling deviations were recorded. The actual sampling times were used in the pharmacokinetic calculations. The blood sampling time deviations were insignificant.
3. No subject experienced emesis during the fed study.
4. Subjects that experienced an adverse event did not require the use of concomitant medications during the course of this study.

4.1.2.3 Bioanalytical Results

Table 27. Assay Validation – Within the Fed Bioequivalence Study

A. Ibuprofen

Fed Bioequivalence Study (Study No. 155-07) Analyte Name: Ibuprofen								
Parameter	**Standard Curve Samples**							
	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Concentration (ng/mL)	40047.730	34441.048	26691.812	18150.432	9982.738	3993.095	1078.136	500.471
Inter day Precision (% CV)	2.6	3.3	2.7	2.8	2.8	4.0	3.9	1.6
Inter day Accuracy (%Accuracy)	98.2	94.4	99.2	103.5	100.3	105.5	99.2	99.7
Linearity (range of r^2 values)	0.9940 – 0.9994							
Linearity range (ng/mL)	500.471 – 40047.730							
Sensitivity (ng/mL)	500.471							

Fed Bioequivalence Study (Study No. 155-07) Analyte Name: Ibuprofen				
Parameter	**Quality Control Samples**			
	HQC	MQC	M2QC	LQC
Concentration (ng/mL)	32052.291	12820.916	6225.019	1282.092
Inter day precision (%CV)	3.3	4.0	4.0	5.0
Inter day accuracy (% Accuracy)	103.2	107.3	104.8	104.8

B. Diphenhydramine

Fed Bioequivalence Study (Study No. 155-07) Analyte Name: Diphenhydramine								
Parameter	**Standard Curve Samples**							
	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Concentration (ng/mL)	50.344	43.296	32.472	22.73	13.638	5.455	2.564	1.051
Inter day Precision (% CV)	3.8	3.3	2.2	2.6	3.8	4.6	4.5	2.0
Inter day Accuracy (%Accuracy)	100.6	98.1	100.9	101.5	98.5	101.1	98.8	100.3
Linearity (range of r^2 values)	0.9942 – 0.9996							
Linearity range (ng/mL)	1.051 – 50.344							
Sensitivity (ng/mL)	1.051							

Fed Bioequivalence Study (Study No. 155-07) Analyte Name: Diphenhydramine				
Parameter	**Quality Control Samples**			
	HQC	MQC	M2QC	LQC
Concentration (ng/mL)	40.222	18.100	9.050	2.643
Inter day precision (%CV)	4.8	5.1	5.4	5.0
Inter day accuracy (% Accuracy)	102.9	98.9	98.9	97.5

Comments on Study Assay Validation:

Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially (Subjects #23, #24, #25, #26, #27, #28, #29, #30, #31 and #32)

Comments on Chromatograms:

Acceptable

Table 28. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
BR030_04	27 Oct 2006	Repeat Analysis

Table 29. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Agree
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

The study assays are acceptable.

4.1.2.4 Pharmacokinetic Results

Table 30. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 34 and Figure 3

A. Ibuprofen

Fed Bioequivalence Study, Study No. 155-07									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	69939.54	25.95	46013.25	153478.9	68208.58	25.16	44454.11	127677.5	1.03
AUC∞ (hr *ng/ml)	74039.12	30.15	47383.82	175267.2	71319.86	28.61	48008.91	150282.3	1.04
Cmax (ng/ml)	16046.31	20.87	7908.67	24285.57	16700.80	20.72	9263.82	26838.84	0.96
Tmax* (hr)	2.50	.	0.75	6.00	2.00	.	1.00	6.00	1.25
Kel (hr^{-1})	0.37	24.49	0.20	0.72	0.35	18.67	0.19	0.43	1.05
T1/2 (hr)	2.01	26.10	0.97	3.54	2.07	23.00	1.59	3.60	0.97

* Tmax values are presented as median, range

B. Diphenhydramine

Fed Bioequivalence Study, Study No. 155-07									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	368.63	26.49	161.97	586.27	383.89	28.15	215.96	625.43	0.96
AUC∞ (hr *ng/ml)	395.61	25.82	176.06	598.05	417.58	29.09	245.44	749.91	0.95
Cmax (ng/ml)	40.56	35.17	18.20	101.12	41.09	21.83	22.72	63.90	0.99
Tmax* (hr)	2.33	.	0.75	5.50	2.00	.	0.75	5.00	1.17
Kel (hr^{-1})	0.08	19.05	0.05	0.11	0.08	20.21	0.05	0.13	1.01
T1/2 (hr)	8.78	20.13	6.15	12.88	8.90	19.70	5.33	13.72	0.99

* Tmax values are presented as median, range

Table 31. Geometric Means and 90% Confidence Intervals - Firm Calculated

A. Ibuprofen

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. 155-07				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	68165.0105	66501.7112	102.50	98.84 - 106.29
AUC∞ (hr *ng/ml)	71608.6793	69166.2706	103.53	99.87 - 107.33
Cmax (ng/ml)	15700.1737	16347.8606	96.04	90.37 - 102.06

B. Diphenhydramine

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. 155-07				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	354.90	369.70	0.96	90.52 - 101.80
AUC∞ (hr *ng/ml)	381.69	401.79	0.95	89.84 - 100.45
Cmax (ng/ml)	38.56	40.10	0.96	89.02 - 103.86

Note: 90% C.I. values obtained from the firm's study report (155-07) page 484

Table 32. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

A. Ibuprofen

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 155-07					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	68165.01	66501.71	1.03	98.84	106.29
AUC∞ (hr *ng/ml)	71608.68	69166.27	1.04	99.82	107.38
Cmax (ng/ml)	15700.17	16347.86	0.96	90.37	102.06

B. Diphenhydramine

Ibuprofen/Diphenhydramine Caplets 1 x 200 mg/ 38 mg caplet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 155-07					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	354.90	369.70	0.96	90.52	101.80
AUC∞ (hr *ng/ml)	381.69	401.79	0.95	89.84	100.45
Cmax (ng/ml)	38.56	40.10	0.96	89.02	103.86

Table 33. Additional Study Information

Root mean square error, AUC0-t	0.0964 Ibuprofen 0.1558 Diphenhydramine	
Root mean square error, AUC∞	0.0942 Ibuprofen 0.1480 Diphenhydramine	
Root mean square error, Cmax	0.1613 Ibuprofen 0.2045 Diphenhydramine	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	40 Ibuprofen 40 Diphenhydramine	39 Ibuprofen 40 Diphenhydramine
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞					
Treatment		**n**	**Mean**	**Minimum**	**Maximum**
Test	Ibuprofen	40	0.95	0.80	0.98
	Diphenhydramine	40	0.93	0.84	0.98
Reference	Ibuprofen	39	0.95	0.85	0.98
	Diphenhydramine	40	0.92	0.83	0.98

*Note: For Subject # 40, the Kel and AUC∞ could not be determined.

Comments on Pharmacokinetic and Statistical Analysis:

The mean AUCt/AUC∞ ratio >0.9 for both test and reference indicates that the firm's sampling schedule was carried out for a sufficient period of time. All subjects illustrated an AUCt/AUC∞ ratio >0.8 for ibuprofen and diphenhydramine. The SAS program CONTINU was used to verify the firm's data.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fed bioequivalence study on 1 x 200 mg/ 38 mg caplet is incomplete due to inconsistent data for the 90% CI.

Table 34. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Analyte 1 (Ibuprofen)					
Time (hr)	Test (n= 40)		Reference (n= 40)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.25	1423.70	156.26	1030.81	167.93	1.38
0.50	3663.05	115.32	3881.24	116.93	0.94
0.75	5614.15	104.62	6928.73	96.88	0.81
1.00	7057.90	89.91	8504.92	86.77	0.83
1.33	8570.51	76.38	9970.36	67.90	0.86
1.67	9747.00	60.96	11538.79	54.33	0.84
2.00	10337.73	54.38	11572.92	49.51	0.89
2.33	10045.97	47.04	10898.71	47.84	0.92
2.67	10087.57	42.61	10661.58	40.11	0.95
3.00	9836.87	40.72	9967.99	37.44	0.99
3.33	9756.69	38.36	9604.73	34.30	1.02
3.67	10038.92	35.81	9441.80	37.60	1.06
4.00	10116.54	38.43	9508.53	40.27	1.06
4.50	11098.27	39.49	10215.33	44.19	1.09
5.00	9193.11	48.63	8475.63	49.75	1.08
5.50	8228.19	55.21	7258.62	54.21	1.13
6.00	7228.49	55.37	6294.10	55.64	1.15
7.00	5162.16	61.83	4393.64	61.58	1.17
8.00	3697.12	64.50	3150.93	66.20	1.17
10.00	1831.14	79.87	1614.04	85.71	1.13
12.00	1010.57	115.40	813.16	120.63	1.24
24.00	0.00	.	27.13	632.46	0.00
36.00	0.00	.	0.00	.	.

Figure 3. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

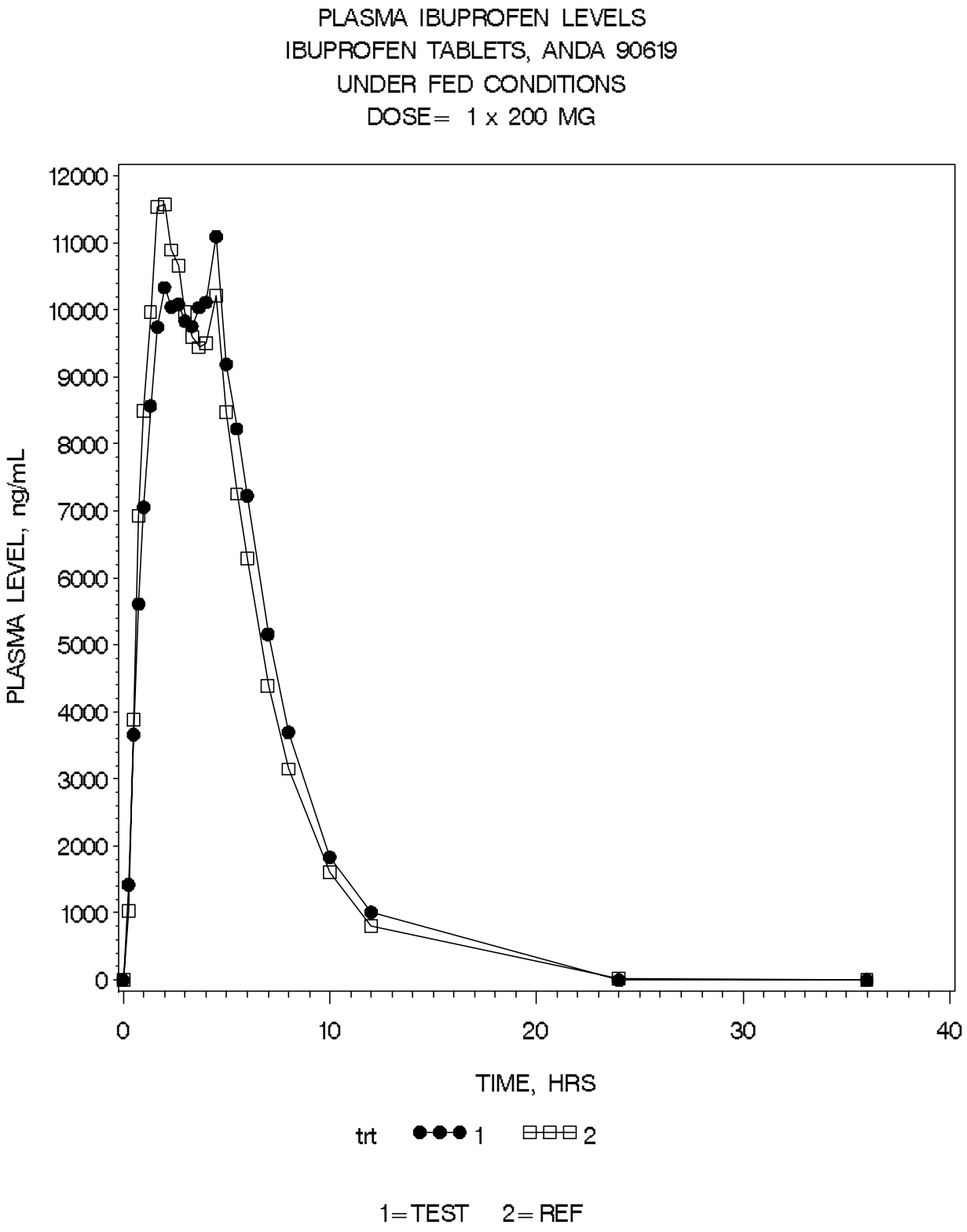
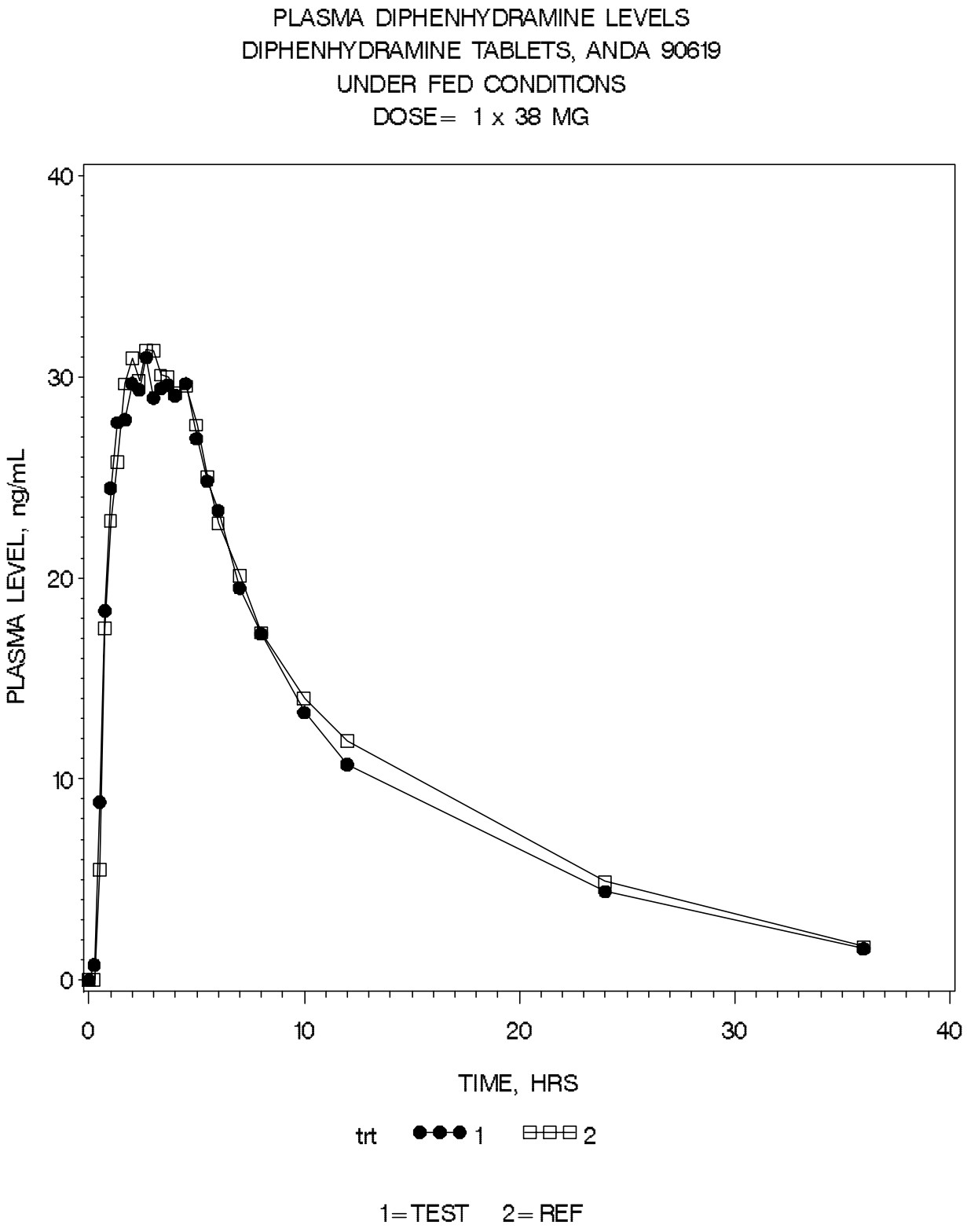


Table 35. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Analyte 1 (Diphenhydramine)					
Time (hr)	Test (n= 40)		Reference (n= 40)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.25	0.75	308.68	0.03	632.46	28.19
0.50	8.86	142.54	5.49	119.71	1.61
0.75	18.37	91.94	17.49	90.56	1.05
1.00	24.47	84.25	22.85	72.30	1.07
1.33	27.74	67.88	25.76	58.08	1.08
1.67	27.88	63.36	29.67	48.31	0.94
2.00	29.68	47.74	30.96	38.70	0.96
2.33	29.36	39.06	29.81	32.27	0.99
2.67	30.98	36.47	31.34	27.55	0.99
3.00	28.97	29.85	31.30	26.84	0.93
3.33	29.43	31.76	30.10	25.59	0.98
3.67	29.60	29.26	29.99	24.81	0.99
4.00	29.08	25.99	29.21	26.13	1.00
4.50	29.68	26.85	29.54	26.01	1.00
5.00	26.94	23.75	27.61	26.01	0.98
5.50	24.82	24.49	25.07	25.52	0.99
6.00	23.36	27.44	22.72	29.70	1.03
7.00	19.51	27.86	20.13	33.70	0.97
8.00	17.23	27.77	17.29	33.16	1.00
10.00	13.31	33.34	14.03	33.88	0.95
12.00	10.73	33.90	11.89	38.14	0.90
24.00	4.41	41.53	4.90	46.10	0.90
36.00	1.56	66.51	1.67	88.88	0.94

Figure 4. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

Ingredient	Amount (mg) / Tablet		Amount (%) / Tablet	
	200/38 mg	NA	200/38 mg	NA
Cores				
Ibuprofen USP	200.000		(b) (4)	
(b) (4)				

Component	mg per tablet	Maximum Potency (mg)	Route of Administration	Pharmaceutical Function
(b) (4)				

Note: Formulation data above is taken from the ANDA checklist review and the IIG limits and CFR limits have been verified by the reviewer. Also, the IIG and CFR limits are within limits based on the Maximum Daily Dose (MDD) of ibuprofen/diphenhydramine, which is 400 mg/day

for ibuprofen and 76 mg/day for diphenhydramine (2 x 200/38 mg) daily for mild pain or insomnia.

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	Acceptable. The quantities of the inactive ingredients in the test products, based on the maximum daily dose (MDD) of 400/76 mg ibuprofen/diphenhydramine are within the limits recommended in FDA's inactive ingredients database. Also, all colors are within the IIG limits and CFR limits.

4.3 Dissolution Data

Dissolution Review Path	DFS: N 090619 N 000 13-Jun-2008

Table 36. Dissolution Data

A. Ibuprofen

Dissolution Conditions	**Apparatus:**	USP apparatus II (paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 6.5 Phosphate Buffer (50 mM)
	Volume:	900 ml
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	**For Ibuprofen:** Not less than (b) (4) (Q) of the labeled amount of Ibuprofen is dissolved in (b) (4) minutes	
Dissolution Testing Site (Name, Address)	Dr. Reddy's Laboratories Limited (Generics), Located at Bachepalli – 502 325, INDIA	

Study Ref No.	**Testing Date (dd/mm/year)**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**				**Study Report Location**
						10 min	**20 min**	**30 min**	**45 min**	
BN00334	26/02/2008	Advil ® PM Caplets (Ibuprofen, 200mg and Diphenhydramine Citrate, 38 mg Caplets) Batch No: B65608 Exp. date: April 2009	200/38 mg, Caplets	12	Mean	96	99	99	99	Module 5.3.1.3
					Range	95-98	97-101	97-101	97-101	
					%CV	0.9	1.1	1.0	0.9	
BN00320	23/02/2008	Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg, Batch No: EC8063, Mfg. date: February 2008	200/38 mg, Caplets	12	Mean	97	99	99	99	
					Range	96-99	97-100	97-101	97-101	
					%CV	0.9	1.0	1.1	1.1	

B. Diphenhydramine

Dissolution Conditions	**Apparatus:**	USP apparatus II (paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 6.5 Phosphate Buffer (50 mM)
	Volume:	900 ml
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	**For Diphenhydramine Citrate:** Not less than (b)(4)% (Q) of the labeled amount of Diphenhydramine Citrate is dissolved in (b)(4) minutes	
Dissolution Testing Site (Name, Address)	Dr. Reddy's Laboratories Limited (Generics), Located at Bachepalli – 502 325, INDIA	

Study Ref No.	**Testing Date (dd/mm/year)**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**				**Study Report Location**
						10 min	**20 min**	**30 min**	**45 min**	
BN00334	26/02/2008	Advil ® PM Caplets (Ibuprofen, 200mg and Diphenhydramine Citrate, 38 mg Caplets) Batch No: B65608 Exp. date: April 2009	200/38 mg, Caplets	12	Mean	100	101	101	101	Module 5.3.1.3
					Range	96-103	97-105	96-104	96-103	
					%CV	2.1	2.4	2.3	2.3	
BN00320	23/02/2008	Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg, Batch No: EC8063, Mfg. date: February 2008	200/38 mg, Caplets	12	Mean	96	97	97	97	
					Range	95-98	96-99	95-99	95-99	
					%CV	0.9	1.0	1.2	1.1	

4.4 Detailed Regulatory History (If Applicable)

None

4.5 Consult Reviews

None

124 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI) IMMEDIATELY FOLLOWING THIS PAGE

Contains Nonbinding Recommendations

Draft Guidance on Ibuprofen/ Diphenhydramine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Ibuprofen and Diphenhydramine Citrate Caplets

Form/Route: Caplets/Oral

Recommended studies: 1 study

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 200 mg/ 38 mg
   Subjects: Normal healthy males and females, general population. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study.

Analytes to measure (in appropriate biological fluid): Parent compounds, ibuprofen and diphenhydramine in plasma

Bioequivalence based on (90% CI): Ibuprofen and diphenhydramine

Waiver request of *in-vivo* testing: Not applicable

Dissolution test method and sampling times:
Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Please note that a dosage unit for a suspension is the labeled strength (5 ml). A total of 12 units from 12 different bottles should be used. Specifications will be determined upon review of the application.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 90-619

APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Ibuprofen/Diphenhydramine Citrate Caplets, 200 mg/38 mg (OTC)

The Division of Bioequivalence (DBE) has completed its review of your submissions acknowledged on the cover sheet. The following deficiency has been identified:

You submitted two (2) different sets of 90% Confidence Interval (CI) summary data for diphenhydramine in the fed study (155-07). The 90% CI values you submitted in your **Table 3**: Statistical Summary of the Comparative Bioavailability Data of 155-07 (Fed study) is inconsistent with the 90% CI values submitted in your study report (page 484), which were based on your statistical analysis of diphenhydramine in the fed study. Please explain this discrepancy.

Table 3: Statistical Summary of the Comparative Bioavailability Data of 155-07 (Fed study)

Ibuprofen + Diphenhydramine citrate 200 mg/38 mg caplets Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study No. 155-07)				
Diphenhydramine				
AUC_{0-INF} (ng*h/mL)	381.6884	401.7938	95.00	89.84 - 100.45
AUC_{0-t} (ng*hr/mL)	354.9011	369.7046	96.00	98.84 - 106.29
C_{max} (ng/mL)	38.5564	40.0983	96.15	90.37 - 102.06

Project No.:155-07 15:07 Monday, May 26, 2008

Statistical Analysis for log transformed PK Parameters of Diphenhydramine

Pkpar	ISCV	lsm_T	lsm_R	Ratio	LCL	UCL	BIOEQUIVALENCE	Power
LnCmax	20.7	38.5564	40.0983	96.15	89.02	103.86	YES	99.9
LnAUC0-T	15.7	354.9011	369.7046	96.00	90.52	101.80	YES	100.0
LnAUC0-INF	14.9	381.6884	401.7938	95.00	89.84	100.45	YES	100.0

We acknowledge that you will conduct the dissolution testing using the following FDA-recommended method and specification:

The dissolution testing should be conducted in 900 mL of 50 mM Phosphate buffer, pH 6.5 at 37°C ± 0.5°C using USP apparatus 2 (paddle) at 50 rpm. The test product should meet the following specification: Not less than (b) (4) %(Q) of the labeled amount of both drugs (ibuprofen and diphenhydramine) in the dosage form is dissolved in 30 minutes.

Sincerely yours,

{See appended electronic signature page}

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

4.8 Outcome Page

ANDA: 90-619

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod

5 COMPLETED ASSIGNMENT FOR 90619 ID: 7952

Reviewer: Johnson, Glendolynn **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Ibuprofen and Diphenhydramine (Dr. Reddy)

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7952	6/13/2008	Bioequivalence Study	Fasting Study	1	1
7952	6/13/2008	Bioequivalence Study	Fed Study	1	1
				Bean Total:	2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Glendolynn S Johnson
4/13/2009 07:26:54 AM
BIOPHARMACEUTICS

Yih Chain Huang
4/13/2009 09:32:16 AM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
4/13/2009 05:12:04 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	90-619 (OTC)	
Drug Product Name	Diphenhydramine Citrate and Ibuprofen Tablet	
Strength (s)	38 mg/200 mg	
Applicant Name	Dr. Reddy's Laboratories Limited	
Address	Mailing Address: Bachepalli, Post Bag No. 15, Kukatpally P.O., Hyderabad - 500 072, India. Factory Address: Bachepalli 502 325, India	
Applicant's Point of Contact	Kumara Sekar, Ph.D., Sr.Director, Global Regulatory Affairs & Compliance	
Contact's Phone Number	704-496-6065	
Contact's Fax Number	704-496-6082	
Submission Date(s)	June 13, 2008	
First Generic	No	
Reviewer	Xiaojian Jiang, Ph.D.	
Study Number (s)	149-07[1]	155-07
Study Type (s)	Fasting	Fed
Strength(s)	38 mg/200 mg	38 mg/200 mg
Clinical Site and Address	GVK BIOSCIENCES PVT LTD., Clinical Pharmacology Unit 7th Floor, Swarna Jayanthi Commercial Complex Ameerpet, Hyderabad – 500 038.	
Analytical Site and Address	(b) (4)	
OUTCOME DECISION	**Incomplete**	

[1] Per the responses to the control document#060321, the DBE recommends only fasting study for approval of generic version of this product.

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

The product references Advil® PM (Diphenhydramine Citrate and Ibuprofen) Caplet, 38 mg/ 200 mg, from Wyeth Cons, NDA 21394.

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable. However, the firm's proposed liberal specifications (NLT (b) (4)% (Q) in (b) (4) min) for both components are not acceptable. The firm should acknowledge the FDA-recommended method and data driven specifications (NLT (b) (4)% (Q) in 30 minutes) for both components which the test product meets at the S1 level for both components.

Note: The current "on-the-file" specification for this products are NLT (b) (4)% (Q) in 30 min for both components.

The firm did not submit the Long Term Storage Stability (LTSS) data for both components. The firm should submit LTSS data for ibuprofen and diphenhydramine that are sufficient to cover the maximum storage time of the study samples (48 and 50 days, respectively for ibuprofen and diphenhydramine).

Both clinical and analytical sites were inspected on 10/26/2007. No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The DBE will review the fasted and fed BE studies at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☒	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☐	☒	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Internal Dissolution Database: Not available

External Dissolution Database

Diphenhydramine Citrate/Ibuprofen	Tablet	II (Paddle)	50	50 mM Phosphate Buffer, pH 6.5	900	10, 20, 30 and 45	01/14/2008

Dissolution method and specification obtained from DBE review of control document# 060321 (V:\FirmsNZ\Perrigo\Controls\060321c0306.doc, reference: OCP Review of NDA 21-394, Submission Date of 11/01/2005).

Medium: 900 mL of 50 mM phosphate buffer, pH 6.5

Apparatus: II (Paddle) at 50 rpm

Sampling: 10, 15, 20, 30 minutes and until at least (b)(4)% of the label amount of the drug is dissolved.

Specification: Q = (b)(4)% at 30 minutes for both components

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Table 5A: Ibuprofen

Dissolution Conditions	**Apparatus:**	USP apparatus II (paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 6.5 Phosphate Buffer (50 mM)
	Volume:	900 ml
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	**For Ibuprofen:** Not less than (b)(4)% (Q) of the labeled amount of Ibuprofen is dissolved in (b)(4)minutes	
Dissolution Testing Site (Name, Address)	Dr. Reddy's Laboratories Limited (Generics), Located at Bachepalli – 502 325, INDIA	

Study Ref No.	Testing Date (dd/mm/year)	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10 min	20 min	30 min	45 min	Study Report Location
BN00334	26/02/2008	Advil® PM Caplets (Ibuprofen, 200mg and Diphenhydramine Citrate, 38 mg Caplets) Batch No: B65608 Exp. date: April 2009	200/38 mg, Caplets	12	Mean	96	99	99	99	Module 5.3.1.3
					Range	95-98	97-101	97-101	97-101	
					%CV	0.9	1.1	1.0	0.9	
BN00320	23/02/2008	Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg, Batch No: EC8063, Mfg. date: February 2008	200/38 mg, Caplets	12	Mean	97	99	99	99	
					Range	96-99	97-100	97-101	97-101	
					%CV	0.9	1.0	1.1	1.1	

Table 5B: Diphenhydramine Citrate

Dissolution Conditions	**Apparatus:**	USP apparatus II (paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 6.5 Phosphate Buffer (50 mM)
	Volume:	900 ml
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	**For Diphenhydramine Citrate:** Not less than (b)(4) % (Q) of the labeled amount of Diphenhydramine Citrate is dissolved in (b)(4) minutes	
Dissolution Testing Site (Name, Address)	Dr. Reddy's Laboratories Limited (Generics), Located at Bachepalli – 502 325, INDIA	

Study Ref No.	Testing Date (dd/mm/year)	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10 min	20 min	30 min	45 min	Study Report Location
BN00334	26/02/2008	Advil ® PM Caplets (Ibuprofen, 200mg and Diphenhydramine Citrate, 38 mg Caplets) Batch No: B65608 Exp. date: April 2009	200/38 mg, Caplets	12	Mean	100	101	101	101	Module 5.3.1.3
					Range	96-103	97-105	96-104	96-103	
					%CV	2.1	2.4	2.3	2.3	
BN00320	23/02/2008	Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg, Batch No: EC8063, Mfg. date: February 2008	200/38 mg, Caplets	12	Mean	96	97	97	97	
					Range	95-98	96-99	95-99	95-99	
					%CV	0.9	1.0	1.2	1.1	

II. COMMENTS:

The dissolution testing is acceptable. However, the firm's proposed specifications for both components (NLT (b) (4)% (Q) released in (b) (4) minutes) are liberal. The firm will be requested to accept the data driven specifications of NLT (b) (4)% (Q) in 30 minutes for both components. The test product meets these specifications for both components at the S1 level.

III. DEFICIENCY COMMENT:

1. The firm should acknowledge the FDA recommended method and data driven specifications.

2. The firm did not submit the Long Term Storage Stability (LTSS) data for both components. The firm should submit LTSS data for ibuprofen and diphenhydramine that are sufficient to cover the maximum storage time of the study samples for ibuprofen and diphenhydramine (48 and 50 days, respectively).

IV. RECOMMENDATION:

The *in vitro* dissolution testing conducted by the firm on the test and reference products is acceptable. However, the firm's proposed dissolution specifications are not acceptable. The dissolution testing should be conducted in 900 ml of 50 mM Phosphate Buffer, pH 6.5 at 37°C using USP apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

Not less than (b) (4)% (Q) of the labeled amount of drug in the dosage form is dissolved in 30 minutes for Ibuprofen and Diphenhydramine Citrate.

BIOEQUIVALENCE DEFICIENCY

ANDA: 90-619

APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Diphenhydramine Citrate and Ibuprofen Tablet, 38 mg/200 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted at a later date. The following deficiencies have been identified:

1. Your dissolution testing is acceptable. However, your proposed specifications (NLT (b)(4)% (Q) in (b)(4) minutes) for both components are not acceptable. The dissolution testing should be conducted in 900 mL of 50 mM Phosphate Buffer, pH 6.5 at 37°C using USP Apparatus II (paddles) at 50 rpm. The test product should meet the following specification:

   NLT (b)(4)% (Q) of the labeled amount of ibuprofen and Diphenhydramine citrate in the dosage form is dissolved in **30 minutes**.

   Your dissolution data meet the FDA-recommended specifications listed above. Please acknowledge your acceptance of the FDA-recommended dissolution method and specifications.

2. Please provide long term storage stability data of ibuprofen and diphenhydramine in frozen plasma to cover the maximum storage period of the study samples, which is at least 48 and 50 days respectively for ibuprofen and diphenhydramine.

Sincerely yours,

{See appended electronic signature page}

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

V. OUTCOME

Completed Assignment for 90619 ID: 7005

Reviewer: Jiang, Xiaojian **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: ?

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7005	6/13/2008	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Xiaojian Jiang
12/11/2008 11:52:45 AM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
12/11/2008 12:36:58 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
12/12/2008 10:59:14 AM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-619

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 90-619 Applicant Dr. Reddy's Laboratories, Ltd
Drug Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg Strength(s)

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 6 July 2009 Date 7/8/09
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92)
Pediatric Exclusivity System
RLD = Advil PM NDA# 21-394
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked N/A
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 6/16/2008, BOS=Advil PM NDA 21394, no relevant patent certification provided. ANDA ack for filing on 6/16/2008(LO dated 8/20/2008). There are no remaining patents or exclusivities remaining for this drug product. NC exclusivity expired on 12/21/2008. ANDA is eligible for Full Approval.

2. Project Manager, Dat Doan Team1 Review Support Branch Date 6/26/09 Date _____
Initials dd Initials _____

Original Rec'd date 6/13/08
Date Acceptable for Filing 6/16/08
Patent Certification (type) I
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/30/09
Date of Office Bio Review 5/8/09
Date of Labeling Approv. Sum 6/25/09
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement

Reviewer:
Date_____
Name/Initials_____

Labeling Team Leader:
Date 7/8/09
Name/Initials rlw/for

Comments:

From: Lee, Koung U
Sent: Wednesday, July 01, 2009 2:11 PM
To: Barlow, James T; Doan, Dat
Subject: RE: 90-619/Ibuprofen & Diphenhydramine/DRL

Dat,

I concur.

Koung

From: Barlow, James T
Sent: Wednesday, July 01, 2009 2:10 PM
To: Doan, Dat; Lee, Koung U
Subject: RE: 90-619/Ibuprofen & Diphenhydramine/DRL

I checked Drugs@FDA,OB and USP.
The labeling Approval Summary signed by Koung Lee on 6/25/09 remains acceptable.

From: Doan, Dat
Sent: Wednesday, July 01, 2009 1:24 PM
To: Barlow, James T; Lee, Koung U
Subject: 90-619/Ibuprofen & Diphenhydramine/DRL
Importance: High

HI Koung, Jim:

Can I please get your endorsement for ANDA 90-619/Ibuprofen & Diphenhydramine/DRL?

<< File: 90619.ap.letter.DOC >>

<< File: 90619.ap.labeling.summary.pdf >>

Thanks,

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 7/8/09
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments: N/A. There are no patents listed in the current "Orange Book" for this drug product.

5. Div. Dir./Deputy Dir. Date7/7/09
Chemistry Div. I II OR III Initials RMP
Comments:CMC satisfactory for AP.

6. Frank Holcombe **First Generics Only** Date 7/8/09
Assoc. Dir. For Chemistry Initials rlw/for Comments: (First generic drug review)
N/A. Perrigo R&D's ANDA 79-113 for this drug product was approved on 12/22/08.

7. Vacant Date_____ Deputy Dir., DLPS
Initials_____
RLD = Advil PM Tablets 200 mg/38 mg
Wyeth Consumer Healthcare NDA 21-394

8. Peter Rickman Date 7/8/09
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐ Comments: Bioequivalence studies (fasting and non-fasting) found acceptable.
In-vitro dissolution testing also found acceptable. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 5/8/09.

Final-printed labeling (FPL) found acceptable for approval 6/25/09.

CMC found acceptable for approval (Chemistry Review #2).

OR

8. Robert L. West Date 7/8/09
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 4/30/09 (Verified 7/8/09). No "OAI" Alerts noted.

There are no unexpired patents or exclusivity listed in the current "Orange Book"

for this drug product.

This ANDA is recommended for approval.

9. Gary Buehler Date 7/8/09
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Dat Doan Date7/8/09
Review Support Branch Initials dd

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
2:39pmTime notified of approval by phone
2:39pm Time approval letter faxed

FDA Notification:
7/8/09 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
7/8/09 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

EES Data for: 090619

*** Compliance Recommendations ***

App No	Doc Seq No	Date	OC Recommendation
090619	000	4/30/2009	ACCEPTABLE
090619	000	11/12/2008	ACCEPTABLE

*** EER Table ***

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert/ Effective Date
(b) (4)	(b) (4)	TCM	OC RECOMMENDATION	3/9/2009	AC	3/9/2009	None
2311630	DR REDDY'S LABORATORIES LOUISIANA L	TCM	OC RECOMMENDATION	3/9/2009	AC	3/9/2009	None
(b) (4)	(b) (4)	CSN	OC RECOMMENDATION	11/12/2008	AC	11/12/2008	None
9617573	DR. REDDY'S LABORATORIES, UNIT III	TCM	OC RECOMMENDATION	8/29/2008	AC	8/29/2008	None
9617573	DR. REDDY'S LABORATORIES, UNIT III	CSN	OC RECOMMENDATION	8/18/2008	AC	8/18/2008	None

COMIS TABLE:

Comis Application Table Data for Application No: 090619

***** Note: For Enterprise Search Files you may have to click and close the new window on first use***

Back to Search Form | ***COMIS Pool Reviewers*** | **ES DFS Files Only** | **ES - All Files** | **EDR** | **Cycles**

Drug Name: IBUPROFEN AND DIPHENHYDRAMINE CITRATE

Potency: 200MG/38MG Dosage Form: TAB APPL Type: N

Applicant: DR REDDYS LABS INC

Status Code: PN Status Date: 2/3/2009 Clock Date: 6/16/2008 USP: Y Org: 600

Therapeutic Drug Class: ACUTE PAIN, NON-OPIOID

Patent Certification: 1 Patent Expiration Date: PEPFAR: N

Incom Doc Type	Seq No	Supp Mod Type	Letter Date	Stamp Date	Decision Code	Decision_Date	Status code	Status Date	Priority Flag	Document ID-Click to see Assignment	Priority Date
N Volume Locator	000		6/13/2008	6/16/2008	NM	11/21/2008	PN	2/3/2009	1	3952403	2/3/2009
N Volume Locator	000	MC	7/17/2008	7/21/2008	CL	7/21/2008				3986439	
N Volume Locator	000	AB	12/12/2008	12/15/2008	OP	12/15/2008				4058036	
N Volume Locator	000	AB	12/30/2008	1/2/2009	OP	1/2/2009				4066206	
N Volume Locator	000	AF	12/26/2008	12/31/2008	OP	12/31/2008				4066395	
N Volume Locator	000	AM	1/29/2009	2/3/2009	OP	2/3/2009				4079876	
N Volume Locator	000	AA	2/26/2009	3/5/2009	OP	3/5/2009				4097237	
N Volume Locator	000	AF	4/10/2009	4/13/2009	OP	4/13/2009				4117967	

N ***Volume Locator***	000	AB	4/17/2009	4/22/2009	OP	4/22/2009				4123432	***Comis Document Table Data***

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 021394 Product 001 in the OB_OTC list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021394	001	NC	Dec 21, 2008

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through May, 2009
Patent and Generic Drug Product Data Last Updated: July 07, 2009

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/s/

Dat Doan
7/8/2009 02:41:07 PM

BIOEQUIVALENCE AMENDMENT

ANDA 90-619

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Dr. Reddy's Laboratories Limited

TEL: (908) 203-4937 or (704) 496-6065

ATTN: Kumara Sekar

FAX: (908) 203-4980 or (704) 496-6082

FROM: Nam J. Chun

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on June 13, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **two** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 90-619

APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Ibuprofen/Diphenhydramine Citrate Caplets, 200 mg/38 mg (OTC)

The Division of Bioequivalence (DBE) has completed its review of your submissions acknowledged on the cover sheet. The following deficiency has been identified:

You submitted two (2) different sets of 90% Confidence Interval (CI) summary data for diphenhydramine in the fed study (155-07). The 90% CI values you submitted in your **Table 3**: Statistical Summary of the Comparative Bioavailability Data of 155-07 (Fed study) is inconsistent with the 90% CI values submitted in your study report (page 484), which were based on your statistical analysis of diphenhydramine in the fed study. Please explain this discrepancy.

Table 3: Statistical Summary of the Comparative Bioavailability Data of 155-07 (Fed study)

Ibuprofen + Diphenhydramine citrate 200 mg/38 mg caplets Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study No. 155-07)				
Diphenhydramine				
AUC_{0-INF} (ng*h/mL)	381.6884	401.7938	95.00	89.84 - 100.45
AUC_{0-t} (ng*hr/mL)	354.9011	369.7046	96.00	98.84 - 106.29
C_{max} (ng/mL)	38.5564	40.0983	96.15	90.37 - 102.06

Project No.:155-07 15:07 Monday, May 26, 2008

Statistical Analysis for log transformed PK Parameters of Diphenhydramine

Pkpar	ISCV	lsm_T	lsm_R	Ratio	LCL	UCL	BIOEQUIVALENCE	Power
LnCmax	20.7	38.5564	40.0983	96.15	89.02	103.86	YES	99.9
LnAUC0-T	15.7	354.9011	369.7046	96.00	90.52	101.80	YES	100.0
LnAUC0-INF	14.9	381.6884	401.7938	95.00	89.84	100.45	YES	100.0

We acknowledge that you will conduct the dissolution testing using the following FDA-recommended method and specification:

The dissolution testing should be conducted in 900 mL of 50 mM Phosphate buffer, pH 6.5 at 37°C ± 0.5°C using USP apparatus 2 (paddle) at 50 rpm. The test product should meet the following specification: Not less than (b)(4) %(Q) of the labeled amount of both drugs (ibuprofen and diphenhydramine) in the dosage form is dissolved in 30 minutes.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Dale Conner

4/15/2009 10:34:22 AM

Telephone Fax

ANDA 90-619

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
james.barlow@fda.hhs.gov

TO: Dr. Reddy Laboratories Limited

TEL: 704-496-6065

ATTN: Kumara Sekar (US Agent)

FAX: 704-496-6082

FROM: Mr Jim Barlow

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen and Diphenhydramine Caplets.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

See attached labeling comments.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	90-619
Date of Submission:	June 13, 2008 **and** December 26, 2008
Applicant's Name:	Dr. Reddys Laboratories
Established Name:	Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

---

Labeling Deficiencies:

1. CONTAINER/CARTON-

a. **General Comments -** Please note that the term "caplet" is not an official USP dosage form classification. Therefore, revise the name of your drug product to read as written below to be in accordance with USP 23. The term "caplet" may be retained in the net quantity statement as long as it is defined as a "capsule-shaped tablet".

b. Front Panel –
Revise to read as follows –

Dr. Reddy's
xx Caplets*
NDC#

Ibuprofen and
Diphenhydramine Citrate
Tablets
200 mg/38 mg

Pain Reliever (NSAID)/**
Nighttime Sleep-Aid

***capsule-shaped tablets**

c. Side Panel –

Active ingredients (in each caplet*)	Purposes
Diphenhydramine citrate 38 mg……..	Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)**	Pain reliever

**nonsteroidal anti-inflammatory drug

d. Please revise labels and labeling to be in accord with the most recently approved labeling for the reference listed drug, Advil PM® (NDA 21-394/S-012; approved June 12, 2008).

e. Please confirm that the correct font size was utilized in the text of your labels and labeling. We refer you to 21 CFR 201.66(d) for guidance referencing OTC format requirements.

f. We note that your proposed 180 and 500 count bottles utilize a non-CRC closure system. As noted in the Consumer Product Safety Commission 16 CFR; part 1700, OTC drug products need to utilize a CRC closure system. Please revise and/or comment.

2. **CONTAINERS – All strengths**

Increase the established name and drug strength to be the most prominent print on the label.

Revise your labeling as requested above and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

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 the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

James Barlow
3/18/2009 01:58:47 PM

BIOEQUIVALENCE AMENDMENT

ANDA 90-619

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Dr. Reddy's Laboratories Limited TEL: (704) 496-6065

ATTN: Kumara Sekar FAX: (704) 496-6082

FROM: Diana Solana-Sodeinde FDA CONTACT PHONE: (240)276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on June 13, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

ANDA: 90-619

APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Diphenhydramine Citrate and Ibuprofen Tablet, 38 mg/200 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted at a later date. The following deficiencies have been identified:

1. Your dissolution testing is acceptable. However, your proposed specifications (NLT (b)(4)% (Q) in (b)(4) minutes) for both components are not acceptable. The dissolution testing should be conducted in 900 mL of 50 mM Phosphate Buffer, pH 6.5 at 37°C using USP Apparatus II (paddles) at 50 rpm. The test product should meet the following specification:

   NLT (b)(4)% (Q) of the labeled amount of ibuprofen and Diphenhydramine citrate in the dosage form is dissolved in **30 minutes**.

   Your dissolution data meets the FDA-recommended specifications listed above. Please acknowledge your acceptance of the FDA-recommended dissolution method and specifications.

2. Please provide long term storage stability data of ibuprofen and diphenhydramine in frozen plasma to cover the maximum storage period of the study samples, which is at least 48 and 50 days respectively for ibuprofen and diphenhydramine.

Sincerely yours,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dale Conner

12/18/2008 08:43:11 AM

COMPLETE RESPONSE -- MINOR

ANDA 90-619

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Dr. Reddy's Laboratories Limited TEL: (704) 496-6065

ATTN: Kumara Sekar FAX: (704) 496-6082

FROM: Dat Doan FDA CONTACT PHONE: (240) 276-8573

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 13, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen and Diphenhydramine Hydrochloride Tablets, 200 mg/38 mg.

SPECIAL INSTRUCTIONS: **please see attached**

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-619 APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/ 38 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug Master File (DMF) (b) (4), has been reviewed and found to be deficient. The deficiencies have been transmitted to the DMF holder. Please do not respond to this deficiency letter until you have received notification from the DMF holder that the deficiencies have been addressed.

2. We note that you have provided RRT and RRF for the Diphenhydramine Citrate impurities (b) (4) in the related substance validation report for the drug product. Please provide COA and source of the (b) (4) with the data to calculate the RRF for the impurities.

3. Please submit the following:
A statement in the Drug Product specification, "Meets USP <467> requirements for residual solvents" along with the method used to establish permitted daily exposure for residual solvents (Options 1 or 2). Also, a statement from the excipient/drug substance manufacturer for the following two scenarios:
(1) If solvents are used in the manufacturing process:
Names of the residual solvents and specifications. Certificates of Analysis (your COAs and the manufactures' COAs)
A statement from the manufacturer stating that no other solvents are used in the manufacturing process.
(2) If solvents are NOT used in the manufacturing process:
A statement from the manufacturer that no solvents are used in the manufacturing process.
Submit copies of the revised drug substance/excipient specifications.

Submit a commitment to re-assess your compliance with USP<467> if you change ingredient suppliers in the post approval period including implementing revised controls, if appropriate.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The bioequivalence information which you have provided is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

2. The labeling portion of your application is currently under review. The Division of Labeling and Program Support will notify you, under separate cover, of all labeling deficiencies.

3. If necessary, the drug product release and stability dissolution specifications may require revision according to recommendations of the Division of Bioequivalence. Please note that if the recommended dissolution test method differs from your initially proposed test method, we will request additional information including stability.

4. We note that you have established optimum amount of each excipient by formulating with a range of amounts, this is acceptable. However, in our opinion this is not considered design space as mentioned in the table in Module 3.2.P.2.2.1. For Design Space you would need to establish effect of all excipients together with varying amount and with interactions.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rosario DCosta

11/21/2008 03:37:04 PM

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 90-619 **FIRM NAME**: DR. REDDY'S LABORATORIES, INC.

PIV: NO **Electronic or Paper Submission:** ELECTRONIC (ECTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: IBUPROFEN AND DIPHENHYDRAMINE CITRATE

DOSAGE FORM: TABLETS, 200 MG/38 MG

Random Queue: 1

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

Chem Team Leader: Mueller, Albert Chem PM: Dat Doan Labeling Reviewer: James Barlow
Bio PM: Beth Fabian-Fritsch

Letter Date: JUNE 13, 2008 **Received Date**: JUNE 16, 2008

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 5030300 ACUTE PAIN, NON-OPIOID

Archival copy: ELECTRONIC (ECTD FORMAT) **Sections** I
Review copy: NA E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Tim Jetton **Date**	**Recommendation:** ☐ **FILE** ☐ **REFUSE to RECEIVE**

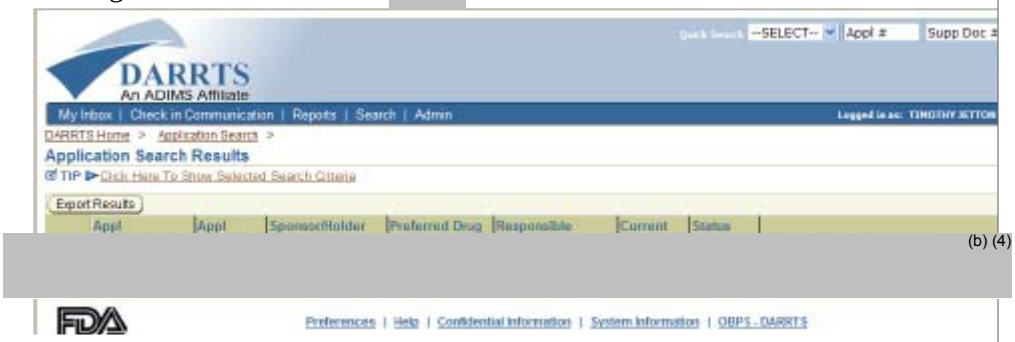
Supervisory Concurrence/Date: ____ **Date:** ____

ADDITIONAL COMMENTS REGARDING THE ANDA:
1. Kumar Sekar 704-496-6065
2. has FORM 3674
3. Environmental Impact analysis needs to reference 21 cfr 25.31 - FOUND
4. Need reprocessing statement. – FOUND
5. Need 12 tablet dissolution breakdown - FOUND

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: JUNE 13, 2008	☒
*	**Table of Contents (paper submission only)** NA - eCTD	☒
1.3.2	**Field Copy Certification (original signature)** NA - **eCTD** **(N/A for E-Submissions)**	☐
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES or Disclosure Statement (Form FDA 3455) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) 021393 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? NA b. Expiration of Pediatric Exclusivity? NA 4. Exclusivity Statement: YES In accordance with 21 CFR §314.94(a)(3)(ii), Dr. Reddy's Laboratories Limited is submitting this statement regarding marketing exclusivities to which the reference listed drug is entitled. Information published in "Approved Drug Products with Therapeutic Equivalence Evaluations," Electronic Version current as of April 2008, lists the following exclusivities to which the referenced listed drug is entitled: • NC: New Combination– Expiry Date: Dec. 21, 2008 Dr. Reddy's Laboratories, Ltd. certifies that it does not intend to market the subject product before Dec. 21, 2008, the date on which the NC exclusivity will expire.	☒

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES – 6669 & (b) (4)   b. Type III DMF authorization letter(s) for container closure YES - (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES	☒
1.12.11	**Basis for Submission** NDA# : 21-394 Ref Listed Drug: ADVIL PM Firm: WYETH ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use YES 2. Active ingredients YES 3. Inactive ingredients YES 4. Route of administration YES 5. Dosage Form YES 6. Strength YES	☒
1.12.14	**Environmental Impact Analysis Statement** YES –	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒

1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically NA – OTC ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained NA - OTC **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** NO A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** YES **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** YES **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation YES Table 6. Formulation Data YES **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution YES **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies YES	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) YES 2. Function or Responsibility YES 3. Type II DMF number for API YES – (b) (4) & 6669 4. CFN or FEI numbers YES (b) (4) & (b) (4)	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2 Analytical Procedures** YES **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) YES – SORT OF Upon request, samples of Drug Substance with appropriate identification will be made available. The samples of Drug Substance is stored as Reserve Samples as per the Standard Operating Procedure. The samples are labeled with name of the Product / Material, A.R. No., Lot No. etc for Identification. **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

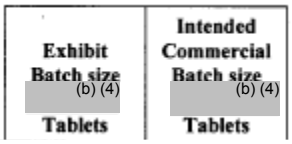
MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition YES 2. Inactive ingredients and amounts are appropriate per IIG YES	☒

(b) (4)

[redacted]

3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2 Batch Formula** YES **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES  **Exhibit Batch size** (b) (4) **Tablets** | **Intended Commercial Batch size** (b) (4) **Tablets** 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement YES **Reprocessing Statement** As a matter of practice, Dr. Reddy's Laboratories Limited does not use reprocessing in the manufacture of their drug products. Dr. Reddy's Laboratories Limited will follow the Current Good Manufacturing Practices as prescribed in '21 CFR part 211.115 – Reprocessing' for reprocessing, if any. **3.2.P.3.4 Controls of Critical Steps and Intermediates** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation na 2. Filter validation (if aseptic fill) na	☐
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** YES **3.2.P.5.2 Analytical Procedures** YES **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: **A. Sample Availability and Identification of Drug Product** Upon request, samples of Finished Dosage Form with appropriate identification will be made available. The samples of Finished Dosage Form are stored as Reserve Samples as per the Standard Operating Procedure. The samples are labelled with name of the Product / Material, A.R. No., Lot No. etc for Identification. **B. Lot / Batch Number of Drug Product (Exhibit Batch):** Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg, Batch No: EC8063 **C. Lot / Batch Number of Drug Product Used for Bio-study:** Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg, Batch No: EC8063 **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES BATCH EC8063 **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period YES Accordingly, a 24-month expiration is requested for Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg for 20's count in (b) (4) containers, 30's count in (b) (4) containers, 40's count in (b) (4) containers, 80's count in (b) (4) container, 90's count in (b) (4) container, 180's count in (b) (4) containers, 500's count in (b) (4) containers, and 12 months as repackaging period for (b) (4) ouch packaging configurations. Controlled room temperature (25°C ± 2°C and 60% ± 5% RH) studies are ongoing to support our proposed expiration dating period. Module 3 **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) YES** **3.2.R.2.S Comparability Protocols YES** **3.2.R.3.S Methods Validation Package YES** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES	☒

Ibuprofen and Diphenhydramine Citrate Caplets, 200/38 mg

Batch# : EC 8063 **Actual Yield :** (b) (4) **Tablets**
Batch Size : (b) (4) **Tablets** **Quantity Packed : Tablets**

Count	Quantity Packed (Tablets)	Reserve Samples (Tablets)	Stability Samples (Tablets)	Bio Samples (Tablets)	Quantity transferred to Ware House (Tablets)
					(b) (4)

3.2.R.1.P.2 Information on Components YES
3.2.R.2.P Comparability Protocols NA
3.2.R.3.P Methods Validation Package YES
Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions)
(Required for Non-USP drugs)

MODULE 5

CLINICAL STUDY REPORTS ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) NA b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) NA **2. Lot Numbers of Products used in BE Study(ies):** YES EC8063 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

5.3.1.2 Comparative BA/BE Study Reports

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)YES ☒

Ibuprofen + Diphenhydramine citrate 200 mg/38 mg caplets Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. 149-07)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
Ibuprofen				
AUC_{0-t} (ngh/mL)	68235.3129	68066.9945	100.25	98.01 - 102.54
AUC_{0-INF}(nghr/mL)	70526.4449	70377.9070	100.21	97.98 - 102.50
C_{max}(ng/mL)	19353.3113	18587.1731	104.12	98.65 - 109.89
Diphenhydramine				
AUC_{0-t} (ngh/mL)	306.8366	304.9641	100.61	94.75 - 106.84
AUC_{0-INF}(nghr/mL)	335.8696	331.4388	101.34	95.99 - 106.99
C_{max}(ng/mL)	32.3377	32.6864	98.93	93.81 - 104.34
Nor- Diphenhydramine				
AUC_{0-t} (ngh/mL)	142.3753	142.6059	99.84	96.69 - 103.09
AUC_{0-INF}(nghr/mL)	168.4645	169.2205	99.55	97.02 - 102.15
C_{max}(ng/mL)	9.2194	9.5552	96.49	93.06 – 100.04

2. Summary Bioequivalence tabl

Ibuprofen + Diphenhydramine citrate 200 mg/38 mg caplets Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study No. 155-07)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
Ibuprofen				
AUC_{0-INF} (ng*h/mL)	71608.6793	69166.2706	103.53	99.87 - 107.33
AUC_{0-t} (ng*hr/mL)	68165.0105	66501.7112	102.50	98.84 - 106.29
C_{max} (ng/mL)	15700.1737	16347.8606	96.04	90.37 - 102.06
Diphenhydramine				
AUC_{0-INF} (ng*h/mL)	381.6884	401.7938	95.00	89.84 - 100.45
AUC_{0-t} (ng*hr/mL)	354.9011	369.7046	96.00	98.84 - 106.29
C_{max} (ng/mL)	38.5564	40.0983	96.15	90.37 - 102.06
Nor - Diphenhydramine				
AUC_{0-INF} (ng*h/mL)	171.8526	180.1504	95.39	92.09 - 98.81
AUC_{0-t} (ng*hr/mL)	142.1796	147.4982	96.39	92.11 - 100.88
C_{max} (ng/mL)	8.6502	8.9687	96.45	92.35 - 100.73

es:

Table 10. Study Information YES
Table 12. Dropout Information YES
Table 13. Protocol Deviations YES

5.3.1.3

In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:
   Table 11. Product Information YES
   Table 16. Composition of Meal Used in Fed Bioequivalence Study YES

5.3.1.4

Reports of Bioanalytical and Analytical Methods for Human Studies

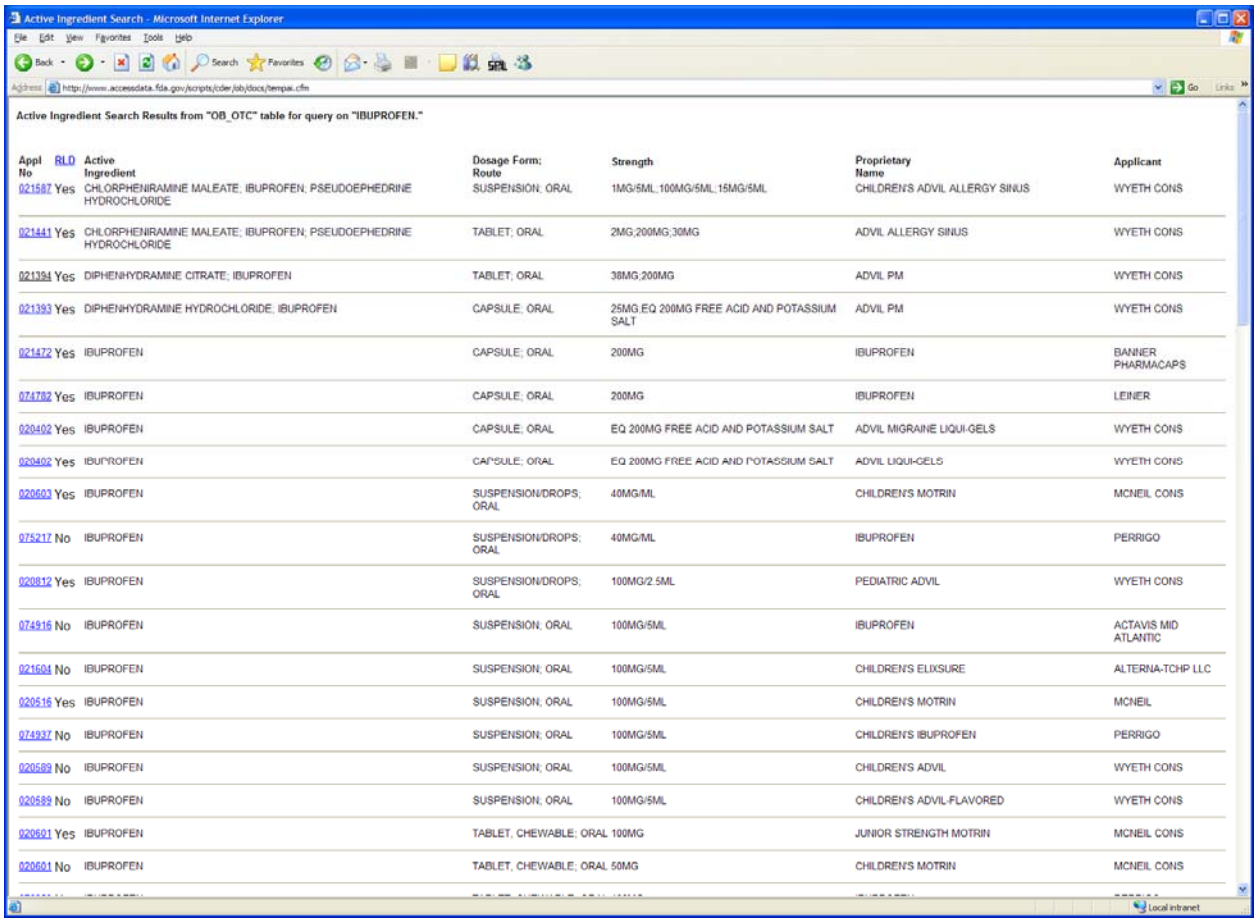
1. Summary Bioequivalence table:
   Table 9. Reanalysis of Study Samples YES
   Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES
   Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES

5.3.7

5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 200 MG/38 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)YES 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution:	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐

Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 5/28/08


Active Ingredient Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
Go Links
Active Ingredient Search Results from "OB_OTC" table for query on "IBUPROFEN."
Appl No
RLD
Active Ingredient
Dosage Form; Route
Strength
Proprietary Name
Applicant
021587 Yes CHLORPHENIRAMINE MALEATE; IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE SUSPENSION; ORAL 1MG/5ML;100MG/5ML;15MG/5ML CHILDREN'S ADVIL ALLERGY SINUS WYETH CONS
021441 Yes CHLORPHENIRAMINE MALEATE; IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE TABLET; ORAL 2MG;200MG;30MG ADVIL ALLERGY SINUS WYETH CONS
021394 Yes DIPHENHYDRAMINE CITRATE; IBUPROFEN TABLET; ORAL 38MG;200MG ADVIL PM WYETH CONS
021393 Yes DIPHENHYDRAMINE HYDROCHLORIDE; IBUPROFEN CAPSULE; ORAL 25MG;EQ 200MG FREE ACID AND POTASSIUM SALT ADVIL PM WYETH CONS
021472 Yes IBUPROFEN CAPSULE; ORAL 200MG IBUPROFEN BANNER PHARMACAPS
074782 Yes IBUPROFEN CAPSULE; ORAL 200MG IBUPROFEN LEINER
020402 Yes IBUPROFEN CAPSULE; ORAL EQ 200MG FREE ACID AND POTASSIUM SALT ADVIL MIGRAINE LIQUI-GELS WYETH CONS
020402 Yes IBUPROFEN CAPSULE; ORAL EQ 200MG FREE ACID AND POTASSIUM SALT ADVIL LIQUI-GELS WYETH CONS
020603 Yes IBUPROFEN SUSPENSION/DROPS; ORAL 40MG/ML CHILDREN'S MOTRIN MCNEIL CONS
075217 No IBUPROFEN SUSPENSION/DROPS; ORAL 40MG/ML IBUPROFEN PERRIGO
020812 Yes IBUPROFEN SUSPENSION/DROPS; ORAL 100MG/2.5ML PEDIATRIC ADVIL WYETH CONS
074916 No IBUPROFEN SUSPENSION; ORAL 100MG/5ML IBUPROFEN ACTAVIS MID ATLANTIC
021604 No IBUPROFEN SUSPENSION; ORAL 100MG/5ML CHILDREN'S ELIXSURE ALTERNA-TCHP LLC
020516 Yes IBUPROFEN SUSPENSION; ORAL 100MG/5ML CHILDREN'S MOTRIN MCNEIL
074937 No IBUPROFEN SUSPENSION; ORAL 100MG/5ML CHILDREN'S IBUPROFEN PERRIGO
020589 No IBUPROFEN SUSPENSION; ORAL 100MG/5ML CHILDREN'S ADVIL WYETH CONS
020589 No IBUPROFEN SUSPENSION; ORAL 100MG/5ML CHILDREN'S ADVIL-FLAVORED WYETH CONS
020601 Yes IBUPROFEN TABLET, CHEWABLE; ORAL 100MG JUNIOR STRENGTH MOTRIN MCNEIL CONS
020601 No IBUPROFEN TABLET, CHEWABLE; ORAL 50MG CHILDREN'S MOTRIN MCNEIL CONS
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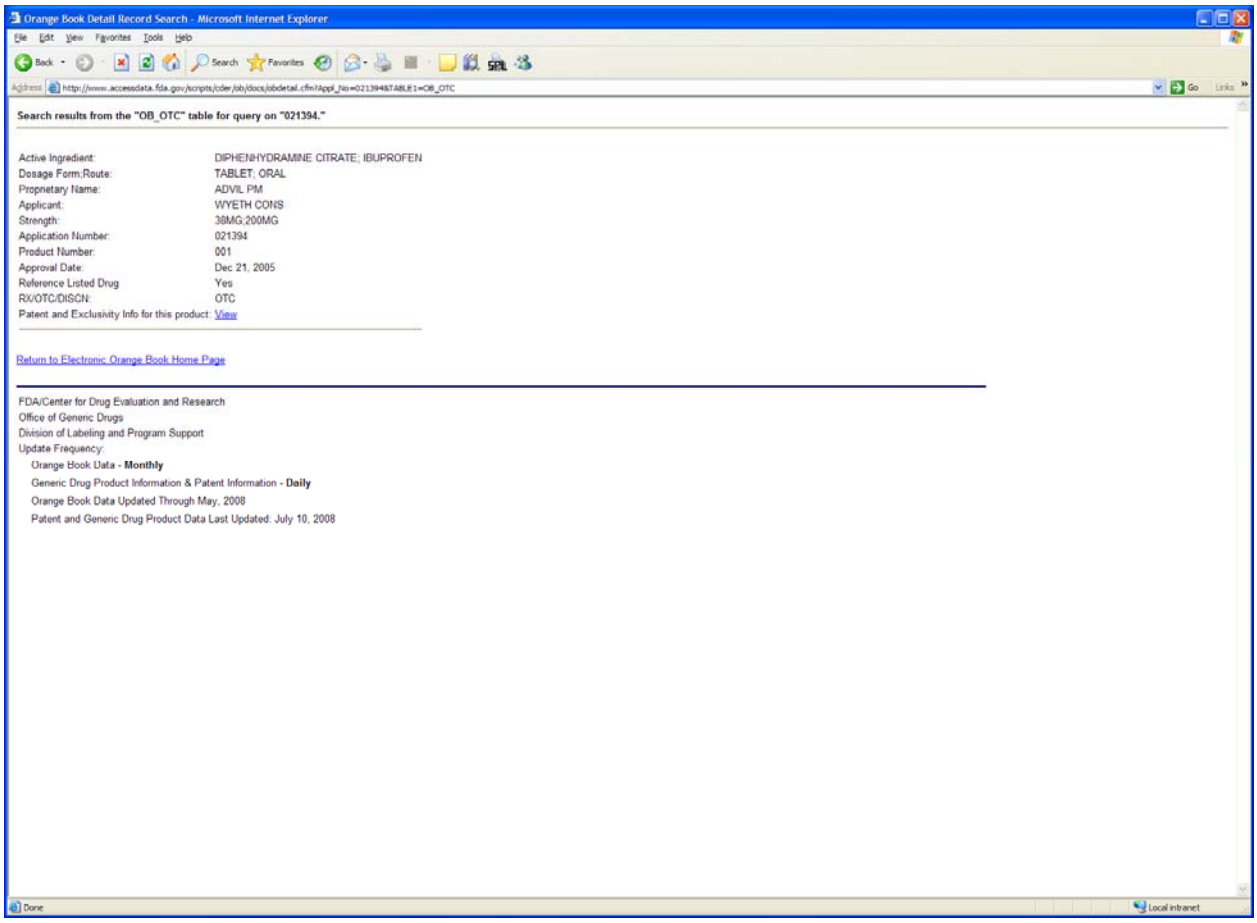
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File Edit View Favorites Tools Help
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Active Ingredient: DIPHENHYDRAMINE CITRATE; IBUPROFEN
Dosage Form;Route: TABLET; ORAL
Proprietary Name: ADVIL PM
Applicant: WYETH CONS
Strength: 38MG;200MG
Application Number: 021394
Product Number: 001
Approval Date: Dec 21, 2005
Reference Listed Drug Yes
RX/OTC/DISCN: OTC
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
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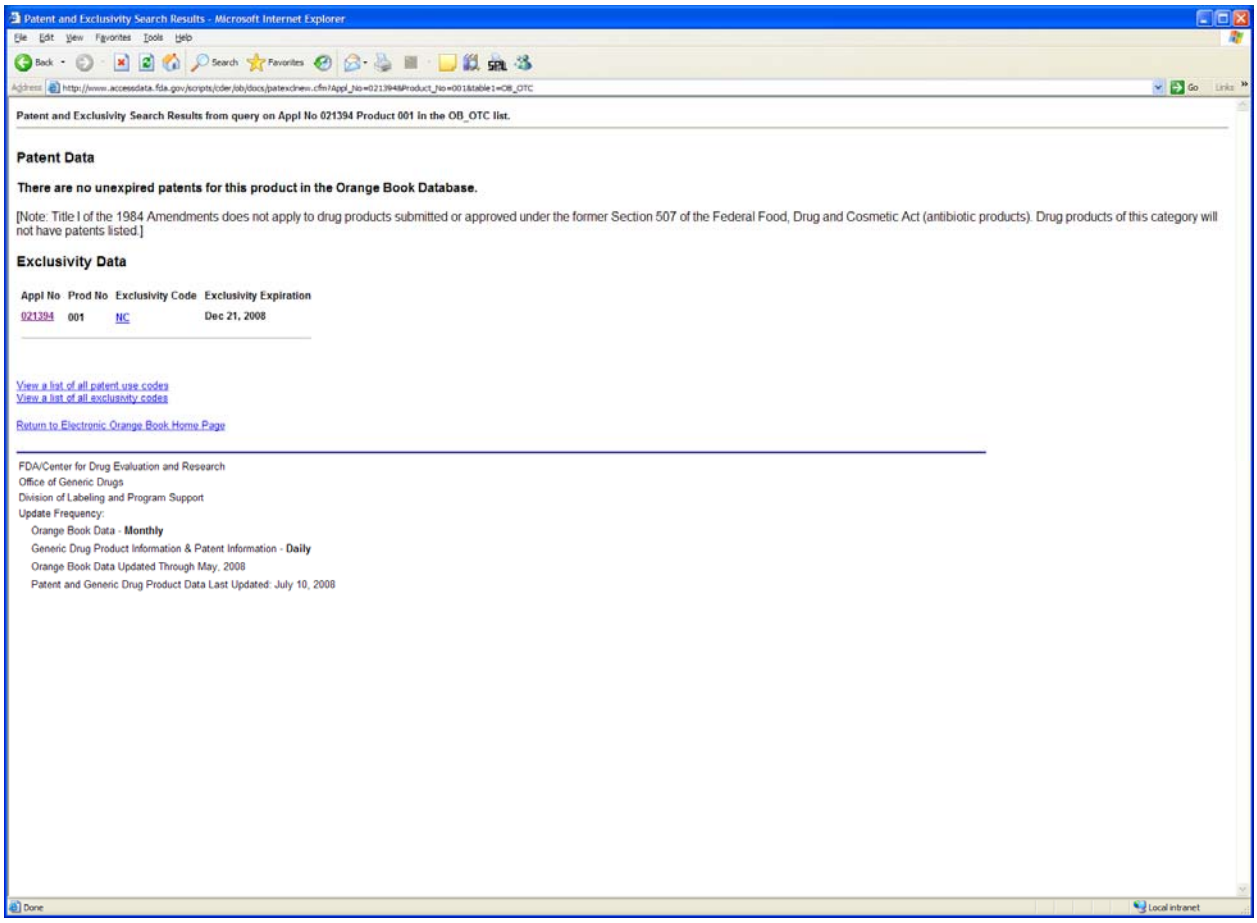
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through May, 2008
Patent and Generic Drug Product Data Last Updated: July 10, 2008
Done
Local intranet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File Edit View Favorites Tools Help
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Patent and Exclusivity Search Results from query on Appl No 021394 Product 001 in the OB_OTC list.
Patent Data
There are no unexpired patents for this product in the Orange Book Database.
[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]
Exclusivity Data
Appl No Prod No Exclusivity Code Exclusivity Expiration
021394 001 NC Dec 21, 2008
View a list of all patent use codes
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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through May, 2008
Patent and Generic Drug Product Data Last Updated: July 10, 2008
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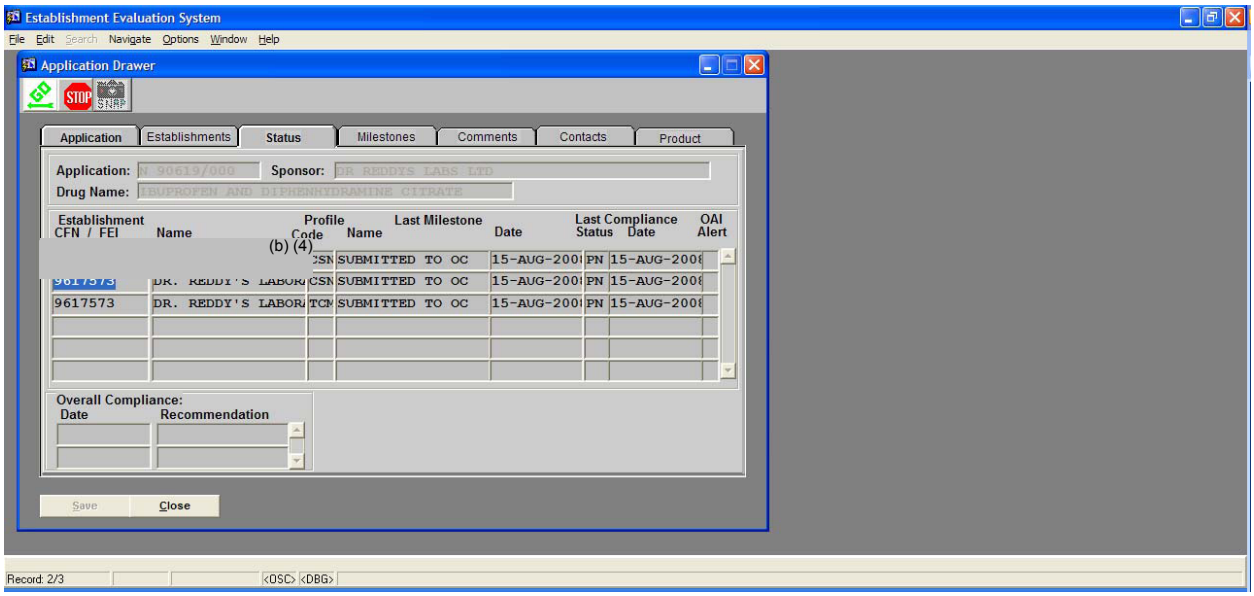
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Application Establishments Status Milestones Comments Contacts Product
Application: N 90619/000 Sponsor: DR REDDYS LABS LTD
Drug Name: IBUPROFEN AND DIPHENHYDRAMINE CITRATE
Establishment CFN / FEI Name
Profile Code
Last Milestone Name
Date
Last Compliance Status
Date
OAI Alert
(b) (4)
CSN SUBMITTED TO OC 15-AUG-2008 PN 15-AUG-2008
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9617573 DR. REDDY'S LABORA TCN SUBMITTED TO OC 15-AUG-2008 PN 15-AUG-2008
Overall Compliance:
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/s/

Martin Shimer

8/20/2008 10:48:56 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-619

Dr. Reddy Laboratories Inc.
Attention: Kumar Sekar, Ph.D.
3600 Arco Corporate Drive, Suite 310
Charlotte, NC 28273-7104

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated August 7, 2008 and your correspondence dated August 14, 2008.

NAME OF DRUG: Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

DATE OF APPLICATION: June 13, 2008

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 16, 2008

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Dat Doan
Project Manager
240-276-8573

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Martin Shimer
8/20/2008 10:48:32 AM
Signing for Wm Peter Rickman