CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-523

Approval Letter

MAR 17 2000

ANDA 75-523

Ranbaxy Laboratories Limited
Attention: Shirley Ternyik
U.S. Agent for: Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

Dear Madam:

This is in reference to your abbreviated new drug application dated December 15, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Pentazocine and Naloxone Hydrochlorides Tablets USP, 50 mg (base) and 0.5 mg (base), respectively.

Reference is also made to your amendments dated September 8, 1999, and February 24, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Pentazocine and Naloxone Hydrochlorides Tablets USP, 50 mg (base)/0.5 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Talwin Nx Tablets, 50 mg (base) and 0.5 mg (base), respectively, of Sanofi Synthelabo). 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 abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-523

FINAL PRINTED LABELING

PENTAZOCINE and NALOXONE HYDROCHLORIDES TABLETS, USP

Analgesic for Oral Use Only
Rx only

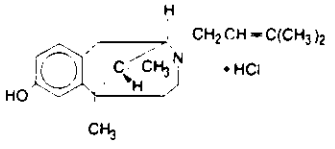
Pentazocine and naloxone hydrochlorides tablets are intended for oral use only. Severe, potentially lethal, reactions may result from misuse of pentazocine and naloxone hydrochlorides by injection either alone or in combination with other substances. (See DRUG ABUSE AND DEPENDENCE section.)

DESCRIPTION

Pentazocine and naloxone hydrochlorides tablets, USP contain pentazocine hydrochloride, USP, equivalent to 50 mg base and is a member of the benzazocine series (also known as the benzomorphan series), and naloxone hydrochloride, USP, equivalent to 0.5 mg base.

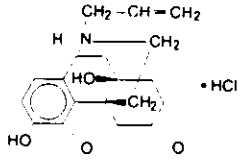
Pentazocine and naloxone hydrochlorides tablets, is an analgesic for oral administration.

Chemically, pentazocine hydrochloride is (2*R**,6*R**,11*R**)- 1, 2, 3, 4, 5, 6-Hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride, a white, crystalline substance soluble in acidic aqueous solutions, and has the following structural formula:



$C_{19}H_{27}NO \cdot HCl$ M.W. = 321.88

Chemically, naloxone hydrochloride is 17-Allyl-4,5α-epoxy-3,14-dihydroxy-morphinan-6-one hydrochloride. It is a slightly off-white powder, and is soluble in water and dilute acids, and has the following structural formula:



$C_{19}H_{21}NO_4 \cdot HCl$ M.W. = 363.84

Each tablet, for oral administration, contains pentazocine hydrochloride, USP, equivalent to 50 mg of pentazocine, and naloxone hydrochloride, USP, equivalent to 0.5 mg of naloxone. In addition, each tablet contains the following inactive ingredients: Colloidal Silicon Dioxide, Corn Starch, Dibasic Calcium Phosphate, D&C Yellow #10 Aluminum lake, Magnesium Stearate, Microcrystalline Cellulose, Sodium Lauryl Sulfate.

CLINICAL PHARMACOLOGY

Pentazocine is a potent analgesic which when administered orally in a 50 mg dose appears equivalent in analgesic effect to 60 mg (1 grain) of codeine. Onset of significant analgesia usually occurs between 15 and 30 minutes after oral administration, and duration of action is usually three hours or longer. Onset and duration of action and the degree of pain relief are related both to dose and the severity of pretreatment pain. Pentazocine weakly antagonizes the analgesic effects of morphine and meperidine; in addition, it produces incomplete reversal of cardiovascular, respiratory, and behavioral depression induced by morphine and meperidine. Pentazocine has about 1/50 the antagonistic activity of nalorphine. It also has sedative activity.

Pentazocine is well absorbed from the gastrointestinal tract. Concentrations in plasma coincide closely with the onset, duration, and intensity of analgesia; peak values occur 1 to 3 hours after oral administration. The half-life in plasma is 2 to 3 hours.

Pentazocine is metabolized in the liver and excreted primarily in the urine. Pentazocine passes into the fetal circulation.

Naloxone when administered orally at 0.5 mg has no pharmacologic activity. Naloxone hydrochloride administered parenterally at the same dose is an effective antagonist to pentazocine and a pure antagonist to narcotic analgesics.

Pentazocine and naloxone hydrochlorides tablets are a potent analgesic when administered orally. However, the presence of naloxone in pentazocine and naloxone hydrochlorides will prevent the effect of pentazocine if the product is misused by injection.

Studies in animals indicate that the presence of naloxone does not affect pentazocine analgesia when the combination is given orally. If the combination is given by injection the action of pentazocine is neutralized

INDICATIONS AND USAGE

Pentazocine and naloxone hydrochlorides tablets are intended for oral use only. Severe, potentially lethal, reactions may result from misuse of pentazocine and naloxone hydrochlorides by injection either alone or in combination with other substances. (See DRUG ABUSE AND DEPENDENCE section.)

Pentazocine and naloxone hydrochlorides tablets are indicated for the relief of moderate to severe pain.

Pentazocine and naloxone hydrochlorides tablets are indicated for oral use only.

CONTRAINDICATIONS

Pentazocine and naloxone hydrochlorides tablets, should not be administered to patients who are hypersensitive to either pentazocine or naloxone.

WARNINGS

Pentazocine and naloxone hydrochlorides tablets are intended for oral use only. Severe, potentially lethal, reactions may result from misuse of pentazocine and naloxone hydrochlorides by injection either alone or in combination with other substances. (See DRUG ABUSE AND DEPENDENCE section.)

Drug Dependence. Pentazocine can cause a physical and psychological dependence. (See DRUG ABUSE AND DEPENDENCE.)

Head Injury and Increased Intracranial Pressure. As in the case of other potent analgesics, the potential of pentazocine for elevating cerebrospinal fluid pressure may be attributed to CO_2 retention due to the respiratory depressant effects of the drug. These effects may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, pentazocine can produce effects which may obscure the clinical course of patients with head injuries. In such patients, pentazocine must be used with extreme caution and only if its use is deemed essential.

Usage with Alcohol. Due to the potential for increased CNS depressants effects, alcohol should be used with caution in patients who are currently receiving pentazocine.

Patients Receiving Narcotics. Pentazocine is a mild narcotic antagonist. Some patients previously given narcotics including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving pentazocine.

Certain Respiratory Conditions. Although respiratory depression has rarely been reported after oral administration of pentazocine, the drug should be administered with caution to patients with respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma, and other obstructive respiratory conditions, or cyanosis.

Acute CNS Manifestations. Patients receiving therapeutic doses of pentazocine have experienced hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted, it should be done with caution since these acute CNS manifestations may recur.

PRECAUTIONS

CNS Effect. Caution should be used when pentazocine is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of pentazocine though no cause and effect relationship has been established.

Impaired Renal or Hepatic Function. Decreased metabolism of pentazocine by the liver in extensive liver disease may predispose to accentuation of side effects. Although laboratory tests have not indicated that pentazocine causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment.

In prescribing pentazocine for long-term use, the physician should take precautions to avoid increases in dose by the patient.

Biliary Surgery. Narcotic drug products are generally considered to elevate biliary tract pressure for varying periods following their administration. Some evidence suggests that pentazocine may differ from other marketed narcotics in this respect (i.e., it causes little or no elevation in biliary tract pressures). The clinical significance of these findings, however, is not yet known.

Information for Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. Pentazocine may cause physical and psychological dependence when taken alone and may have additive CNS depressant properties when taken in combination with alcohol or other CNS depressants.

Myocardial Infarction. As with all drugs, pentazocine should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Drug Interactions. Usage with Alcohol: See WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No long-term studies in animals to test for carcinogenesis have been performed with the components of pentazocine and naloxone hydrochlorides tablets.

Pregnancy Category C. Animal reproduction studies have not been conducted with pentazocine and naloxone hydrochlorides. It is also not known whether pentazocine and naloxone hydrochlorides can cause fetal harm when administered to pregnant women or can affect reproduction capacity. Pentazocine and naloxone hydrochlorides should be given to pregnant women only if clearly needed. However, animal reproduction studies with pentazocine have not demonstrated teratogenic or embryotoxic effects.

Labor and Delivery. Patients receiving pentazocine during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Pentazocine and naloxone hydrochlorides should be used with caution in women delivering premature infants. The effect of pentazocine and naloxone hydrochlorides on the mother and fetus, the duration of labor and delivery, the possibility that forceps delivery or other intervention or resuscitation of the newborn may be necessary, or the effect of pentazocine and naloxone hydrochlorides on the later growth, development, and functional maturation of the child are unknown at the present time.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pentazocine and naloxone hydrochlorides are administered to a nursing woman.

Pediatric Use. Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS

Cardiovascular. Hypotension, tachycardia, syncope.

Respiratory. Rarely, respiratory depression.

Acute CNS Manifestations. Patients receiving therapeutic doses of pentazocine have experienced hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since these acute CNS manifestations may recur.

Other CNS Effects. Dizziness, lightheadedness, hallucinations, sedation, euphoria, headache, confusion, disorientation; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, depression; and rarely tremor, irritability, excitement, tinnitus.

Autonomic. Sweating; infrequently flushing; and rarely chills

Gastrointestinal. Nausea, vomiting, constipation, diarrhea, anorexia, rarely abdominal distress.

Allergic. Edema of the face; dermatitis, including pruritus; flushed skin, including plethora; infrequently rash, and rarely urticaria.

Ophthalmic. Visual blurring and focusing difficulty.

Hematologic. Depression of white blood cells (especially granulocytes), which is usually reversible, moderate transient eosinophilia.

Other. Headache, chills, insomnia, weakness, urinary retention, paresthesia.

DRUG ABUSE AND DEPENDENCE

Controlled Substance. Pentazocine and naloxone hydrochlorides tablet is a Schedule IV controlled substance.

There have been some reports of dependence and of withdrawal symptoms with orally administered pentazocine. Patients with a history of drug dependence should be under close supervision while receiving pentazocine orally. There have been rare reports of possible abstinence syndromes in newborns after prolonged use of pentazocine during pregnancy.

There have been instances of psychological and physical dependence on parenteral pentazocine in patients with a history of drug abuse and rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral pentazocine has resulted in withdrawal symptoms

In prescribing pentazocine for chronic use, the physician should take precautions to avoid increases in dose by the patient.

The amount of naloxone present in pentazocine and naloxone hydrochlorides (0.5 mg per tablet) has no action when taken orally and will not interfere with the pharmacologic action of pentazocine. However, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics.

Severe, even lethal, consequences may result from misuse of tablets by injection either alone or in combination with other substances, such as pulmonary emboli, vascular occlusion, ulceration and abscesses, and withdrawal symptoms in narcotic dependent individuals.

Pentazocine and naloxone hydrochlorides tablets contains an opioid antagonist, naloxone (0.5 mg). Naloxone is inactive when administered orally at this dose, and its inclusion in pentazocine and naloxone hydrochlorides tablet is intended to curb a form of misuse of oral pentazocine. Parenterally, naloxone is an active narcotic antagonist. Thus, pentazocine and naloxone hydrochlorides tablets have a lower potential for parenteral misuse than the previous oral pentazocine hydrochloride formulation. However, it is still subject to patient misuse and abuse by the oral route.

OVERDOSAGE

Manifestations. Clinical experience of overdosage with this oral medication has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. For respiratory depression due to overdosage or unusual sensitivity to pentazocine, parenteral naloxone is a specific and effective antagonist.

DOSAGE AND ADMINISTRATION

Pentazocine and naloxone hydrochlorides tablets are intended for oral use only. Severe, potentially lethal, reactions may result from misuse of pentazocine and naloxone hydrochlorides by injection either alone or in combination with other substances. (See DRUG ABUSE AND DEPENDENCE section.)

Adults. The usual initial adult dose is 1 tablet every three or four hours. This may be increased to 2 tablets when needed. Total daily dosage should not exceed 12 tablets.

When anti-inflammatory or antipyretic effects are desired in addition to analgesia, aspirin can be administered concomitantly with this product.

Children Under 12 Years of Age. Since clinical experience in children under 12 years of age is limited, administration of this product in this age group is not recommended.

Duration of Therapy. Patients with chronic pain who receive pentazocine and naloxone hydrochlorides orally for prolonged periods have not only rarely been reported to experience withdrawal symptoms when administration was abruptly discontinued (see WARNINGS). Tolerance to the analgesic effect of pentazocine has also been reported only rarely. However, there is no long-term experience with the oral administration of pentazocine and naloxone hydrochlorides.

HOW SUPPLIED

Pentazocine and Naloxone Hydrochlorides Tablets, USP (capsule-shaped), light yellow tablets, debossed with "M118" on one side and a score line on the other side, each containing pentazocine hydrochloride equivalent to 50 mg base and naloxone hydrochloride equivalent to 0.5 mg base.

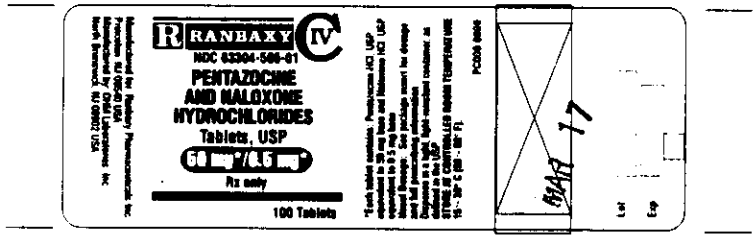
Bottles of 100 (NDC 63304-506-01).

Store at controlled room temperature 15° C to 30° C (59° F to 86° F).

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540 USA
Manufactured by:
OHM Laboratories, Inc.
North Brunswick, NJ 08902 USA

August 1999

PI006


RANBAXY
C IV
NDC 63304-566-01
PENTAZOCINE
AND NALOXONE
HYDROCHLORIDES
Tablets, USP
Rx only
100 Tablets
PC008 9906
Lot
Exp

046

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-523

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA #75-523

3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Pharmaceuticals Inc.
Attention: Shirley Ternyik
U.S. Agent for Ranbaxy Laboratories Ltd.
600 College Road East
Princeton, NJ 08540

4. BASIS OF SUBMISSION
To the best of the applicant's knowledge, no patent claims or marketing exclusivities are in effect (page 10).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Pentazocine HCl/Naloxone HCl

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

9. AMENDMENTS AND OTHER DATES:
December 15, 1998-- Original Submission
January 19, 1999-- New Correspondence
January 11, 1999-- Acknowledgment letter
January 29, 1999-- Bio review, acceptable
March 2, 1999-- Labeling review, unacceptable
August 2, 1999-- Deficiency letter
September 8, 1999-- Amendment

10. PHARMACOLOGICAL CATEGORY
Analgesic

11. Rx or OTC
Rx

12. RELATED DMFs

13. DOSAGE FORM
Tablets

14. POTENCY
50 mg (base)/0.5 mg (base)

15. CHEMICAL NAME AND STRUCTURE
Pentazocine: 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methno-3-benzazocin-8-ol hydrochloride

16. RECORDS AND REPORTS
The drug substance and drug product are compendial articles. The RLD and the applicant's drug product are scored.

17. COMMENTS
Naloxone is inactive when administered orally in the proposed amount of 0.5 mg. It will not interfere with the pharmacological action of Pentazocine. 0.5 mg of naloxone when given by injection has profound antagonistic action to narcotic analgesics. Naloxone is intended to prevent drug abuse since the effect of Pentazocine is neutralized when given by injection.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approvable letter to issue.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
January 14, 2000

1st

Page(s) 10

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #2

1/14/2000

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

8/2/99

Chemistry Comments

#35

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-523

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-523 APPLICANT: Ranbaxy Laboratories Ltd

DRUG PRODUCT: Pentazocíne HCl/Naloxone HCl, 50 mg/0.5 mg Tablets

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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

Sincerely yours,

/S/

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

Pentazocine HCl/Naloxone HCl
50 mg/0.5 mg Tablets
ANDA #75-523
Reviewer: Moheb H. Makary
W #75523sd.D98

Ranbaxy Laboratories Ltd
Gurgaon
Submission date:
December 15, 1998

REVIEW OF TWO BIOSTUDIES AND DISSOLUTION DATA

I. Objective:

The firm has submitted two bioequivalence studies under fasting and nonfasting conditions on its 50 mg/0.5 mg Pentazocine HCl/ Naloxone HCl Tablet and dissolution data to compare the test product relative to Talwin^{R} NX 50 mg/0.5 mg Tablet for review.

II. Background:

This drug is a combination of pentazocine HCl (equivalent to 50 mg base) and naloxone HCl (equivalent to 0.5 mg base). The drug is indicated for oral administration for the relief of moderate and severe pain.

Pentazocine is a synthetic opiate agonist analgesic and its chemical formula is 1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3 methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride.

Naloxone is inactive when administered orally in the amount (0.5 mg) present in this formulation, its presence does not interfere with the pharmacological action of pentazocine when the tablets are administered orally. However, this amount of naloxone given by injection has profound antagonistic action to narcotic analgesics.

The inclusion of naloxone in this drug product is intended to curb a form of misuse of oral pentazocine. The presence of naloxone in this drug product will prevent the effect of pentazocine if the product is misused by injection. Studies in animals indicate that the presence of naloxone does not affect pentazocine analgesia when the combination is given orally. If the combination is given by injection the action of pentazocine is neutralized.

Pentazocine is well absorbed from the gastrointestinal tract. Peak concentrations occur 1 to 3 hours after oral administration. The plasma half-life is 2 to 3 hours. About 60% of pentazocine is bound to plasma proteins. Pentazocine is

metabolized in the liver, mainly by oxidation of the terminal methyl groups of the dimethyl alkyl side chain to form alcoholic and carboxylic acid metabolites; glucuronide conjugation also occurs. There is considerable inter-individual variation in the rate of metabolism and in the accumulative urinary excretion of the drug following oral administration (AHES Drug Information 93).

Pentazocine and Naloxone Hydrochlorides Tablets, 50 mg/0.5 mg is currently marketed under the trade name Talwin® NX Tablets (marketed by

On March 7, 1997
submitted a bioequivalence study protocol (P#97-008) which proposed to measure only pentazocine in the plasma. Naloxone given orally at 0.5 mg dose level is not measurable in the blood, due to first pass metabolism in the liver.

On May 9, 1997 the Division of Bioequivalece issued a letter accepting the protocol and providing some comments. In the Division's response (dated May 9, 1997), the firm's proposal to measure only pentazocine was accepted.

III. Protocol #972664 For Single Dose Fasting Bioequivalence of Ranbaxy's Pentazocine HCl/Naloxone HCl 50 mg/0.5 mg Tablet

Study site:

Study date: Period I August 8, 1998
Period II August 15, 1998

Sample analysis: Sample analysis began on August 18, 1998 and was completed on September 14, 1998.

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

Subjects: Forty-four (44) healthy male subjects entered the study. Forty-three (43) subjects completed the study. Subject #27 elected to withdraw after completing period I for personal reasons. As per protocol, statistical and pharmacokinetic analyses were performed using data from subjects Nos. 1-26, 28-40 and 42.

Dose and Treatments: After a supervised overnight fast (at least 10 hours) subjects received an oral dose of the assigned formulation with 240 mL of water.
Treatment A: 1 x 50 mg/0.5 mg Pentazocine HCl/Naloxone HCl Tablet (Ranbaxy), lot #180357, batch size ablets, potency 100.6%/103.0%, content uniformity 100.5%/102.6%.
Treatment B: 1 x 50 mg/0.5 mg Talwin^{R} NX Tablet (als), lot #B210RP, Exp. 4/2001, potency 100.5%/91.2%, content uniformity 102.0%/91.0%.

Washout period: One week

Selection criteria: Listed in Vol. 1.2, page 115.

Food and fluid intake: Subjects fasted for ten hours prior to dosing until 4 hours after dosing. Water was not allowed from 1 hour before until after drug administration, but was allowed at all other times.

Blood samples: Blood samples were collected at 0 (pre-dose) 0.25, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours after dosing. Plasma samples were immediately frozen

Subject welfare: Vital signs (blood pressure and pulse rate) were measured prior to dosing and within 10 minutes prior to scheduled blood draws at 1, 2, 4, 8 and 12 hours after dosing. Vital signs readings were performed at other times when judged necessary.

Assay Methodology:

Determination of pentazocine in plasma concentrations was performed by

Sensitivity: The limit of quantitation was 0.4 ng/mL for pentazocine.

Linearity: The assay was linear over the concentration range of 0.4 to 150 ng/mL for pentazocine.

Assay specificity: The selectivity of the procedure was verified by analyzing all pre-dose plasma samples for interference at the retention time of pentazocine. No significant interference was observed.

Precision: The precision of the assay was determined by analyzing control samples on each analysis day. The overall coefficient of variation (CV%) ranged from 5.0% to 9.3%.

Accuracy: The average observed concentrations of the control samples were compared to their theoretical concentrations in order to obtain an estimate of accuracy. The overall accuracy ranged from 99.6% to 105.6%.

Recovery: The mean percent recoveries for pentazocine in human plasma at low, medium and high QC concentrations were 97.8%, 103.1% and 103.4%, respectively.

Stability: Long term stability: Pentazocine was stable in human plasma for 106 days at -22°C. Freeze-Thaw: Pentazocine was stable after three freeze-thaw cycles in human plasma. Room Temperature Stability: Pentazocine was stable at the nominal temperature of 20°C for 23.25 hours.

Data Analysis

ANOVA was performed on untransformed AUC(0-t), AUCinf, Cmax, Tmax, kel and t1/2. Additionally, log-transformed data were used for the analysis of AUC(0-t), AUCinf and Cmax. The ANOVA model included sequence, subjects nested within sequence, period and treatment as factors.

IV. In Vivo Results:

Forty-four (44) normal, healthy subjects enrolled in the study. Forty-three (43) subjects successfully completed the clinical portion of the study. As per protocol, statistical and pharmacokinetic analysis were performed using data from forty

(40) subjects. Thirty adverse events were reported in thirteen of forty-four subjects dosed over the course of the study. The adverse events are summarized in page 282, Vol. 1.2. None of the adverse events was considered serious.

The plasma concentrations and pharmacokinetic parameters for pentazocine are summarized in Table I.

Table I

Mean Pentazocine Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1X50 mg/0.5 mg Pentazocine HCl/Naloxone HCl Tablet Under Fasting Conditions
(N=40)

Time hr	Ranbaxy Test Product Lot #180357 ng/mL (CV%)	Sanofi Reference Product Lot #B210RP ng/mL (CV%)
0	0.03 (446)	0.00
0.25	0.08 (282)	0.32 (234)
0.33	0.51 (127)	0.60 (124)
0.5	2.90 (96.6)	3.32 (100)
0.75	9.69 (90.0)	11.51 (89.4)
1	16.73 (83.9)	18.92 (76.6)
1.33	24.45 (70.0)	24.74 (64.9)
1.67	23.77 (63.1	24.95 (59.3)
2	24.41 (58.7)	25.11 (61.8)
2.5	24.59 (66.4)	25.55 (63.3)
3	24.27 (67.5)	24.07 (64.1)
3.5	22.80 (65.9)	22.38 (64.4)
4	21.83 (73.9)	21.00 (64.4)
5	19.31 (77.2)	19.28 (67.5)
6	16.70 (79.3)	17.28 (70.6)
8	11.46 (92.2)	12.17 (91.9)
10	8.24 (100)	8.48 (88.9)
12	6.39 (103)	6.57 (103)
16	4.45 (113)	4.31 (106)
24	2.46 (138)	2.42 (138)

Arithmetic Means

	Test	Reference	% Difference	90% CI log-transf
AUC(0-t) (ng.hr/mL)	225.8(82.0)	229.3(76.2)	0.98	89.6-100.8
AUCinf (ng.hr/mL)	266.1(93.6)	266.4(87.2)	1.00	90.2-101.6
Cmax (ng/mL)	30.0(65.0)	30.4(59.5)	0.99	86.0-104.8
Tmax (hr)	2.03	2.09		
Kel(1/hr)	0.107	0.109		
t1/2 (hr)	7.26	6.91		

1. For Ranbaxy test product, the Least Squares Means AUC(0-t), AUCinf and Cmax values are 1.5%, 0.04% and 1.4% lower, respectively, than those for the reference product values. The differences were not statistically significant. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf and Cmax.

2. The pentazocine plasma levels peaked at 2.5 hours for both the test and the reference products, following their administration under fasting conditions.

3. It should be noted that subjects #20 and #32 vomited at 2.5 and 3.0 hours postdose, respectively. After excluding the two subjects from the statistical analysis of the study, the 90% confidence intervals remained within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf and Cmax.

V. Study #P972674 For Single Dose post-prandial Bioequivalence Study

Objective: The objective of the study is to compare the relative bioavailability of Pentazocine HCl/Naloxone HCl 50 mg/0.5 mg Tablet (Ranbaxy) with that of Talwin^{R} NX 50 mg/0.5 mg Tablet (Sanofi) in healthy male volunteers under-nonfasting conditions, and to compare the difference in plasma levels after dosing with the test product when dosed with and without food.

Study site:

Study design:	Open-label, randomized, 3-way crossover, six-sequence study under fasting and nonfasting conditions.
Dosing dates:	September 24, 1998, Period I October 1, 1998, Period II October 8, 1998, Period III
Analytical Date:	From October 19, 1998 to November 9, 1998
Subjects:	A total of 24 healthy male subjects were enrolled in the study, one did not complete the crossover. Subject #3 elected to withdraw from the study after completion of period II for personal reasons. Thus, a total of 23 subjects completed the crossover. As per protocol, statistical and pharmacokinetic analysis were performed on data from 18 subjects: subject Nos. 1 to 18.
Dose and treatment:	A. 1 x 50 mg/0.5 mg Pentazocine HCl/Naloxone HCl Tablet, lot #180357, manufactured by Ranbaxy Laboratories LTD., under fasting conditions. B. 1 x 50 mg/0.5 mg Pentazocine HCl/Naloxone HCl Tablet, lot #180357, manufactured by Ranbaxy Laboratories LTD., following a standard breakfast. C. 1 x 50 mg/0.5 mg Talwin^{R} NX Tablet, lot #B210RP, manufactured by Sanofi, Inc., following a standard breakfast.
Food and fluid intake:	Subjects on regimens B and C were required to fast overnight until 30 minutes prior to their scheduled dosing times, when they were administered breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice of bacon, 1 buttered English muffin, 1 slice of cheese, 8 ounces of whole milk and 6 ounces of orange juice). Subjects on regimen A were required to fast overnight for 10 hours before dosing and for 4 hours thereafter. Water was not permitted for one hour before until one hour after dosing.

Washout period: One week

Blood samples: Same as the fasting study.

Analytical Methodology

Same as the study above.

Data Analysis

ANOVA was performed with subjects within sequence, period, drug (i.e. formulations), and sequence as factors for AUC(0-t), AUCinf, Cmax and Tmax. Area under the curve was determined using linear trapezoidal method.

VI. In Vivo Results:

Twenty-four (24) volunteers were recruited in the study. A total of 23 subjects completed the crossover of the study. Nine adverse events were reported in seven of the twenty-four subjects dosed over the course of the study. None of the adverse events resulted in dropping any subject from the study, nor they were considered serious (all adverse events are summarized in Vol. 1.7, page 1574).

The plasma concentrations and pharmacokinetic parameters for pentazocine are summarized in Table II.

Table II

Mean Pentazocine Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1X50 mg/0.5 mg Pentazocine HCl/Naloxone HCl Tablet Under Fasting and Nonfasting Conditions
(N=18)

Time hr	Ranbaxy Test Product Lot #180357 Fasting ng/mL (CV%)	Ranbaxy Test Product Lot #180357 Nonfasting ng/mL (CV%)	Sanofi Reference Product Lot #B210RP Nonfasting ng/mL (CV%)
0	0.00	0.00	0.00
0.25	0.24 (280)	0.08 (295)	0.27 (287)
0.33	0.61 (202)	0.52 (315)	0.62 (257)
0.5	3.27 (130)	1.59 (151)	2.34 (205)
0.75	8.29 (84.6)	6.21 (112)	8.64 (141)
1	12.18 (68.7)	12.10 (154)	11.23 (93.4)

1.33	16.33 (73.8)	16.53 (91.1)	18.95 (74.0)
1.67	16.85 (61.4)	21.19 (75.7)	21.49 (65.0)
2	17.32 (55.9)	19.96 (65.5)	24.24 (54.2)
2.5	16.24 (50.4)	22.19 (61.1)	24.48 (46.0)
3	15.96 (53.4)	21.75 (51.1)	23.18 (42.6)
3.5	13.92 (51.5)	20.74 (55.9)	22.78 (40.1)
4	13.22 (52.3)	18.83 (50.6)	20.41 (39.2)
5	11.57 (53.2)	17.28 (53.9)	17.48 (42.5)
6	9.52 (53.7)	13.23 (55.2)	13.86 (46.4)
8	6.57 (53.7)	9.15 (61.0)	9.65 (60.7)
10	4.47 (42.7)	6.22 (54.6)	6.43 (44.6)
12	3.18 (45.3)	4.30 (65.4)	4.47 (46.7)
16	1.94 (55.5)	2.47 (55.5)	2.52 (50.5)
24	0.98 (59.5)	1.15 (65.9)	1.20 (49.4)

				B/C
AUC(0-t) (ng.hr/mL)	130.5(50.2)	173.0(54.0)	183.8(42.8)	0.94
AUCinf (ng.hr/mL)	139.9(50.0)	187.6(54.0)	194.7(42.8)	0.96
Cmax (ng/mL)	19.6(59.8)	27.8(67.5)	29.3(42.3)	0.95
Tmax (hr)	2.07	2.75	2.17	
Kel(1/hr)	0.124	0.126	0.123	
t1/2 (hr)	5.91	5.71	5.84	

1. The pentazocine plasma levels peaked at 2.5 hours for both the test and the reference products under nonfasting conditions and at 2 hours for the test product under fasting conditions.

2. For Ranbaxy's test product, the mean AUC(0-t), AUCinf and Cmax values were 5.90%, 3.65% and 5.12% lower, respectively, than the reference product values under nonfasting conditions. The ratios of the arithmetic and geometric means for pentazocine are within the acceptable range of 0.8-1.2 and 0.8-1.25, respectively, under nonfasting conditions for the above parameters.

3. For the test product, the mean AUC(0-t) and Cmax values after dosing with food increased by 32.6% and 41.8%, respectively, compared to the values reported in the fasting state.

4. Subject #3 elected to withdraw from the study after completion of period II for personal reasons. After excluding him from the statistical analysis of the study, the ratios of the arithmetic and geometric means for for the AUC(0-t), AUCinf and Cmax for pentazocine remained within the acceptable

range under nonfasting conditions.

VII. Formulation:

The Formulation of the test product (mg/tablet) is shown below:

Components	mg/Tablet
Total tablet weight	200.00

VIII. In Vitro Dissolution Testing: (USP Method)

Method:	USP 23 apparatus II (paddle) at 50 rpm
Medium:	900 mL of Water
Number of Tablets:	12
Test products:	Ranbaxy 's Pentazocine HCl/Naloxone HCl 50 mg/0.5 mg Tablets, lot #180357
Reference products:	Sanofi's Talwin^{R} NX 50 mg/0.5 mg mg Tablets, lot #B210RP

Specifications:

Dissolution testing results are shown in Table III.

IX. Comments:

1. The firm's in vivo bioequivalence studies under fasting and nonfasting conditions are acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions for Pentazocine. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax under nonfasting conditions.

2. The dissolution testing is acceptable.

X. Recommendations:

1. The bioequivalence studies conducted by Ranbaxy Laboratories Ltd., under fasting and nonfasting conditions on its Pentazocine HCl/Naloxone HCl, 50 mg/0.5 mg Tablet, lot #180357, comparing it to Sanofi's Talwin^{R} NX, 50 mg/0.5 mg Tablet have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Ranbaxy's Pentazocine HCl/Naloxone HCl Tablet, 50 mg/0.5 mg is bioequivalent to the reference product, Talwin^{R} NX, 50 mg/0.5 mg Tablet, manufactured by Sanofi.

2. The dissolution testing conducted by the firm on its Pentazocine HCl/Naloxone HCl Tablets, 50 mg/0.5 mg, lot #180357, is acceptable.

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

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, Ph.D. Date: 1/29/99
Review Branch III
Division of Bioequivalence

/S/

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT /S/ Date: 1/29/99

Concur: /S/ Date: 2/5/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Table III. In Vitro Dissolution Testing

Drug (Generic Name): Pentazocine HCl and Naloxone HCl
Dose Strength: 50 mg/0.5 mg
ANDA No.: 75-523
Firm: Ranbaxy
Submission Date: December 15, 1998
File Name: 75523sd.D98

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications
pentazocine is
Reference Drug: Sanofi Winthrop's Talwin® NX Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Prod. Pentazocine HCl and Naloxone HCl Lot # 180357 Dissolution of the active ingredient: Pentazocine HCl Strength(mg) 50			Reference Product Sanofi Winthrop's Talwin® NX Lot # B210RP Dissolution of the active ingredient: Pentazocine HCl Strength(mg) 50		
	Mean %	Range	%C	Mean %	Range	%C
10	85		7.1	80		8.9
20	89		4.8	86		5.8
30	91		4.4	89		4.2
45	93		3.4	92		3.0
60	93		2.9	93		2.5

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-523 APPLICANT: Ranbaxy Laboratories Ltd

DRUG PRODUCT: Pentazocine HCl/Naloxone HCl, 50 mg/0.5 mg Tablets

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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

Sincerely yours,

/S/

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

Figure 2

Project No. 972664

Mean Plasma Pentazocine Concentrations

(Linear Plot)

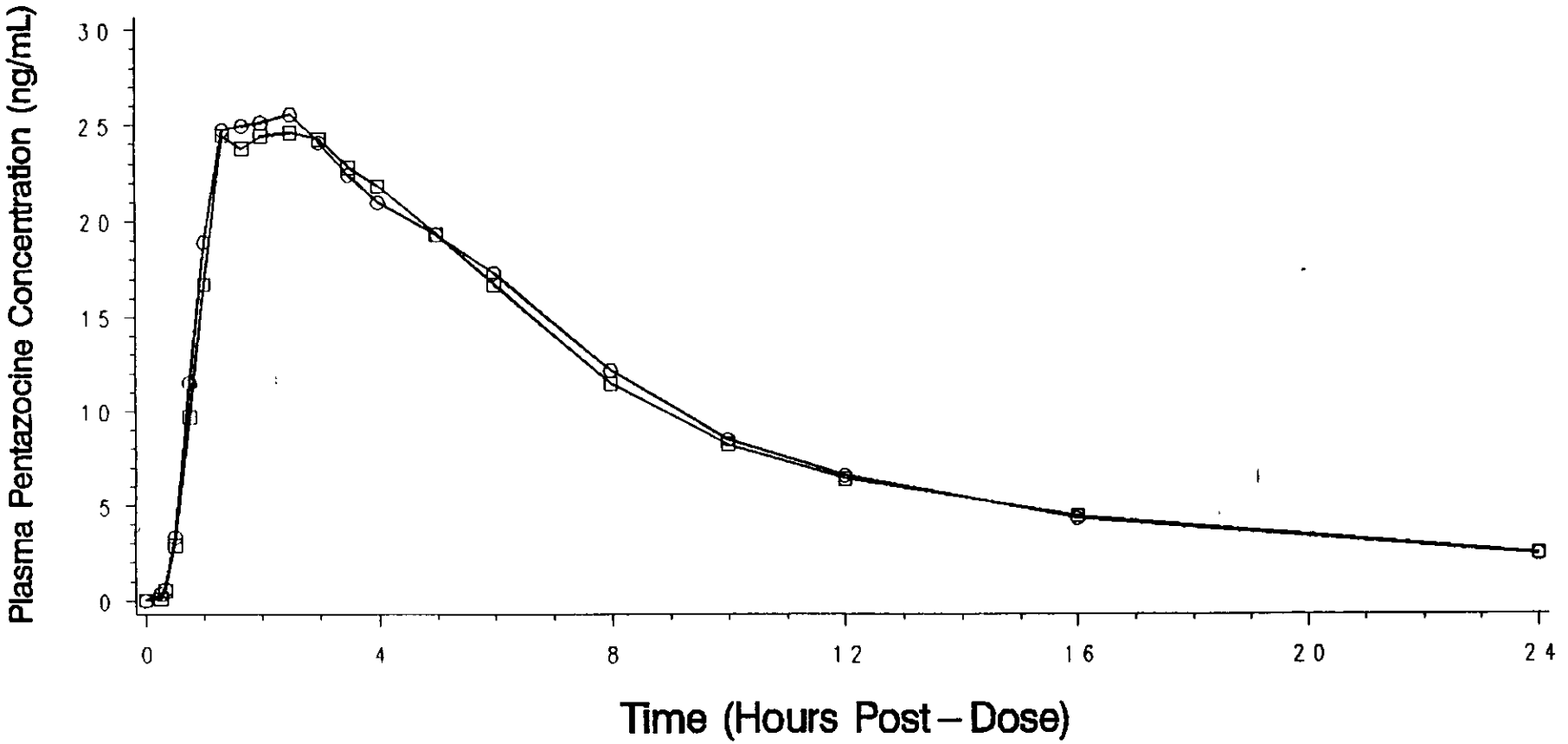
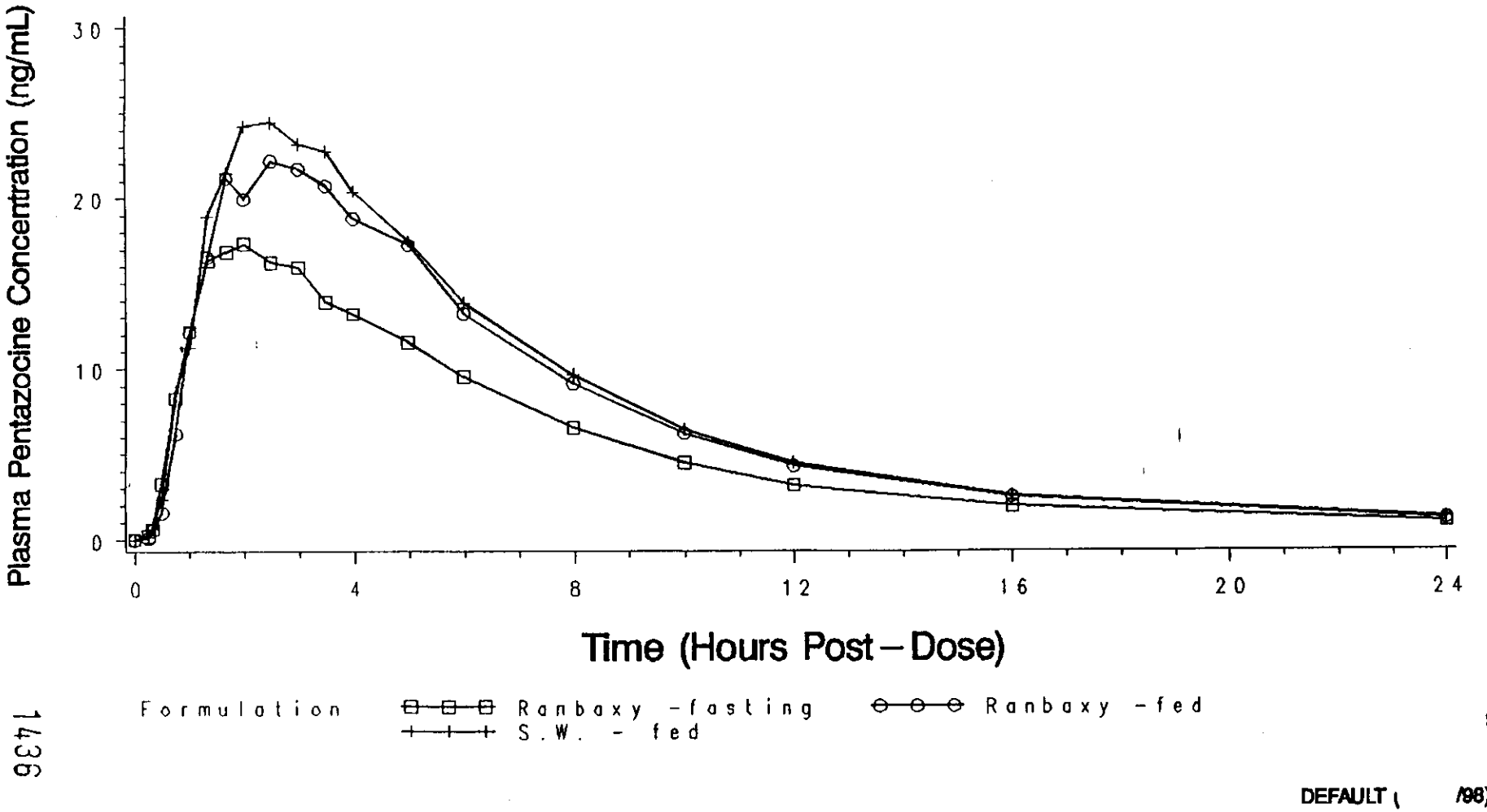


Figure 2

Project No. 972674

Mean Plasma Pentazocine Concentrations

(Linear Plot)



1436

DEFAULT (/98)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-523 APPLICANT: Ranbaxy Laboratories Ltd

DRUG PRODUCT: Pentazocine HCl/Naloxone HCl, 50 mg/0.5 mg Tablets

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-523

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 75-523

DRUG PRODUCT: Pentazocine Hydrochloride/Naloxone Hydrochloride

FIRM: Ranbaxy Pharmaceuticals
DOSAGE FORM: Tablets
STRENGTHS: 50 mg (base) and 0.5 mg (base)
CONTAINER: 40-cc/100's

CGMP STATEMENT/EIR UPDATE STATUS:
Acceptable dated 7/28/99.

BIO INFORMATION:
Acceptable dated 1/29/99.

VALIDATION
Compendial product.

STABILITY
Lot no. 180357 was placed in accelerated (40°C/75% RH) and room temperature stability studies in the proposed marketing container configuration including the bulk packaging. The stability data appended are found to conform to the proposed stability specifications. Based upon the stability data submitted, the proposed 24 months expiration period for the finished product and six months holding period for the bulk container is granted.

The proposed marketing container/closure systems are described in the application.

LABELING
Acceptable dated 9/22/99.

STERILIZATION VALIDATION
N/A

SIZE OF BIO/STABILITY BATCHES
Pentazocine HCl and Naloxone HCl are manufactured by Inc., respectively. DMF were reviewed and found to be adequate on 1/24/00.

50 mg/0.5 mg-demonstration lot no.

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

specifications

2/11/00

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

ANDA Number: 75-523 - Date of Submission: **December 15, 1998**

Applicant's Name: **Ranbaxy Pharmaceuticals Inc.**

Established Name: **Pentazocine and Naloxone Hydrochlorides Tablets USP, 50 mg (base)/0.5 mg (base)**

Labeling Deficiencies:

1. GENERAL COMMENT

We acknowledge your comments that you have submitted draft labeling for both Ranbaxy Pharmaceuticals Inc. and We request, however, that in your next submission you choose one labeling format for our review and comment. All distributor labeling should be based on the labeling approved with your application and a representative sample of distributor labeling may be submitted in your annual reports.

2. CONTAINER 100s

Please revise the controlled substance symbol so that it appears as a separate entity. It lacks prominence and is obscured by the Ranbaxy vignette. Please refer to 21 CFR 201.15(a)(6) for further guidance.

3. INSERT

a. GENERAL COMMENTS

i. There is no need to capitalize and bold the established name throughout the text of the insert.

ii. Delete "USP" from the established name except in the title, the first sentence of the DESCRIPTION section and the HOW SUPPLIED section.

b. BOXED TEXT

... are intended for (rather than "is").

c. DESCRIPTION

i. ... contain ... (rather than "contains").

ii. Third paragraph

1. Revise the chemical name of pentazocine hydrochloride as follows:

(2*R**,6*R**,11*R**)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride

2. Revise the chemical name of naloxone hydrochloride as follows:

17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride

iii. Include •HCl with the structural formula of pentazocine hydrochloride

iv. Include the molecular formula and molecular weight for both active ingredients.

v. Last paragraph

1. Each tablet, for oral administration, contains pentazocine hydrochloride, USP, equivalent to 50 mg of pentazocine, and naloxone hydrochloride, USP, equivalent to 0.5 mg of naloxone. In addition, each tablet contains the following inactive ingredients: ...

2. D&C Yellow #10 Aluminum Lake

3. Corn Starch

c. CLINICAL PHARMACOLOGY

i. Third paragraph - ... into the fetal ... (add "the").

ii. Penultimate paragraph

1. Relocate the blank line/space in the penultimate paragraph

2. First sentence - ... tablets are a ... (rather than "is").

3. Second sentence - ... of naloxone in pentazocine and naloxone hydrochlorides will ...

d. INDICATIONS AND USAGE

i. Boxed text

1. ... tablets are intended ...

2. Delete "tablets, USP" in the second occurrence of the established name

ii. First and second paragraphs - ... are indicated for ... (rather than "is").

e. WARNINGS

Boxed text - See comments under INDICATIONS AND USAGE - Boxed text

f. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, Impairment of Fertility

Delete the excess space between "Carcinogenesis" and "Mutagenesis".

ii. Pregnancy Category C

Delete "tablets" (3 instances).

iii. Labor and Delivery

1. Delete "tablets" (3 instances).

2. Last sentence - ... labor and delivery ... (rather than "or").

iv. Nursing Mothers - Delete "tablets".

v. Pediatric Use - ... in pediatric patients ... (rather than "children").

g. DRUG ABUSE AND DEPENDENCE

i. First paragraph - ... tablet ... (rather than "tablets").

ii. Fifth paragraph - Delete "tablets".

iii. Last paragraph

1. First sentence - "opioid" (spelling).

2. Second instance of established name - "tablet" rather than "tablets".

3. Penultimate sentence

a). ... tablets have a ... (rather than "has")

b). ... oral pentazocine hydrochloride formulation. (add "hydrochloride").

c). Delete "(PENTAZOCINE HYDROCHLORIDE TABLETS, USP)"

h. OVERDOSAGE

Treatment - Delete blank line/space.

i. DOSAGE AND ADMINISTRATION

Boxed text

i. ... tablets are intended ... (rather than "is").

ii. Delete the second occurrence of "tablets".

iii. Duration of Therapy - Delete "tablets" (2 instances).

j. HOW SUPPLIED

Pentazocine and Naloxone Hydrochlorides Tablets, USP are capsule-shaped, light yellow tablets, debossed ...

Please revise your container labels and insert labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

_____

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: 100s

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Talwin NX

NDA Number: 18-733

NDA Drug Name: Talwin NX (Pentazocine and Naloxone Hydrochlorides) Tablets

NDA Firm: Sanofi

Date of Approval of NDA Insert and supplement #: 1-12-89 (S-010)

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: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X

Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: – (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X

Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. This review was based on the labeling for Watson's approved ANDA 74-736 - Pentazocine and Naloxone Hydrochlorides Tablets, USP. The Talwin NX file is missing and the labeling is not located in the Approved Drug Files (Excalibur).

2. The inactives were not correctly listed. Firm failed to state the food source of the starch and also failed to state Aluminum Lake (p 2600 v 1.10).

3. is the manufacturer (p 2678 v 1.10).

4. Dispensing/Storage

   USP: Preserve in tight, light-resistant container.

   RLD: Dispense in tight, light-resistant container as defined in the official compendia. (container) CRT (insert)

   ANDA: Dispense in tight, light-resistant container as defined in the USP - CRT (container) CRT (insert)

5. Both the RLD and the ANDA are scored.

6. The description of the tablet is accurate as seen in the HOW SUPPLIED section (p 2868 v 1.10).

7. The drug product will be made available in HDPE 100s containers with CRC lids (p 2794 v 1.10).

Date of Review: 3-2-99 Date of Submission: 12-15-98

Primary Reviewer: Adolph Vezza /S/ Date: 3/5/99

Team Leader: Charlie Hoppes /S/ Date: 3/5/99

cc:

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-523

CORRESPONDENCE

LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

September 8, 1999

ORIG AMENDMENT
AC

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

FEDERAL EXPRESS

MAJOR AMENDMENT

Reference: ANDA 75-523
PENTAZOCINE AND NALOXONE HYDROCHLORIDES TABLETS USP, 50 MG/0.5 MG

Dear Sir/Madam:

Reference is made to the pending ANDA 75-523 for Pentazocine and Naloxone HCl Tablets USP, 50 mg/0.5 mg.

Reference is also made to the FDA Major Deficiency Letter dated August 2, 1999. The questions and responses follow in the same order as in the letter. They are attached.

Field Copy:
We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this amendment has been provided to the Food and Drug Administration New Jersey District Office in Parsippany, New Jersey.

If you have any questions, regarding the submission, please call me at (609) 720-5612 or Pat Strasser at (609)-720-5617.

Sincerely,

Pat Strasser (for)

Shirley Ternyik
US Agent for Ranbaxy Laboratories Limited

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 10 1999
OGD

RANBAXY
LABORATORIES LIMITED
SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, FAX: (91-124) 342017, 342030

January 19, 1999

NEW CORRESP

NC

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

FAX
FEDERAL EXPRESS

TELEPHONE AMENDMENT

Reference: Pentazocine/Naloxone Hydrochlorides Tablets USP
ANDA 75-523

Dear Sir/Madam:

Reference is made to the pending ANDA 75-523 for Pentazocine/Naloxone Hydrochlorides Tablets USP.

Reference is also made to the OGD's telephone request for additional information for the drug substance manufacturer. The correct address of the drug substance manufacturing site for Pentazocine Hydrochloride and Naloxone Hydrochloride is:

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this amendment has been provided to the Food and Drug Administration Newark District Office in Parsippany, New Jersey.

If you have any additional questions, regarding the submission, please call me at (609) 720-5617.

RECEIVED
JAN 21 1999
GENERIC DRUGS

Sincerely,

Pat Strasser

Pat Strasser (Regulatory Affairs Associate) for
Shirley Ternyik
Associate Director of Regulatory Affairs Ranbaxy Pharmaceutical
US Agent for Ranbayx Laboratories Limited

ANDA 75-523

Ranbaxy Pharmaceuticals Inc.
Attention: Shirley Ternyik
U.S. Agent for Ranbaxy Laboratories Ltd.
600 College Road East
Princeton, NJ 08540

JAN 11 1999

Dear Madam:

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 made to the telephone conversation dated December 22, 1998 and your correspondence dated December 22, 1998.

NAME OF DRUG: Pentazocine and Naloxone Hydrochloride Tablets USP, 50 mg/0.5 mg

DATE OF APPLICATION: December 15, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 16, 1998

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:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

RANBAXY
LABORATORIES LIMITED
SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, FAX: (91-124) 342017, 342030

December 15, 1998

Labeling reviewed
drafted 3/2/99
A Vezza

FEDERAL EXPRESS

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

Reference: Pentazocine/Naloxone Tablets USP
Abbreviated New Drug Application

Dear Sir/Madam:

Ranbaxy Laboratories Ltd. herewith submits an abbreviated new drug application (ANDA) for Pentazocine and Naloxone Hydrochlorides Tablets USP, pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA refers to the listed drug, Talwin Nx® tablets which are manufactured by Sanofi Pharmaceuticals, Inc. (formerly Sanofi Winthrop), the holder of NDA 18-733, as listed in the 1998 Approved Drug Products with Therapeutic Equivalence Evaluations, 18th Edition, p. 3-231.

The manufacturer of the Pentazocine and Naloxone Hydrochlorides, USP drug substances used to produce the ANDA batch of the drug product is

This application provides for the manufacture, processing and packaging at The release and stability studies on the finished drug product are also carried out at the same location.
is 100% owned by Ranbaxy Pharmaceuticals Inc. (RPI). RPI is a 100% wholly owned subsidiary of Ranbaxy Laboratories Limited (RLL), the Parent Company and sponsor of this ANDA. Shirley Ternyik is RLL's U.S. Agent and RPI's Associate Director of Regulatory Affairs. This application submitted by RLL will therefore contain information with either RLL, RPI or name on the document. An authorization letter from RLL appointing Shirley Ternyik as the official U.S. Agent and representative for Ranbaxy Laboratories Limited is attached.

RECEIVED
DEC 16 1998
GENERIC DRUGS

The required bioavailability/bioequivalence study was conducted on Pentazocine and Naloxone Hydrochlorides Tablets, USP and Talwin Nx® tablets by [redacted] The study indicates that Pentazocine and Naloxone Hydrochlorides tablets, USP are bioequivalent to Talwin Nx® tablets. The in-vitro dissolution profile for Pentazocine and Naloxone Hydrochlories tablets, USP is comparable to those of Talwin Nx® tablets.

Pentazocine and Naloxone Hydrochlorides tablets are stable and a two year expiration dating is requested. The two year expiration dating of this product is supported by one, two, and three months accelerated stability data (40°C ± 2°C/75% ± 5% relative humidity). The stability studies were conducted under a stability protocol that is in conformance with the current FDA stability guidelines.

The dosage form, active ingredient, uses, directions, warnings, potency and labeling (except Description, How Supplied and Manufacturer Sections) for Pentazocine and Naloxone Hydrochlorides tablets USP, are the same as those for Talwin Nx® tablets.

The ANDA is submitted in eleven volumes

Volume I:	Section I through Section V
Volume II Through Volume IX:	Section VI
Volume X:	Section VII through Section XV
Volume XI:	Section XVI through Section XXI

Please contact the undersigned at 609-720-5612, if you have any questions regarding this submission.

FIELD COPY: We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this submission has been provided to the Office of Generic Drugs.

Sincerely,

Shirley Ternyik

Shirley Ternyik
US Agent for Ranbaxy Laboratories Ltd.