

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

**40-084/S-001; S-002; S-003; S-004;
S-005; S-006; S-007; S-008; S-009;
S-010; S-011; S-012; S-013; S-014;
S-015; S-016; S-017; S-018; S-019;
S-020; S-021; S-022; S-023; S-024;
S-028**

Trade Name: Anexsia

Generic Name: Hydrocodone and Acetaminophen
Tablets, USP, 10mg/660mg, 5mg/500mg,
7.5mg/750mg, 10mg/650mg

Sponsor: Mallinckrodt Chemical, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
40-084/S-001; S-002; S-003; S-004;
S-005; S-006; S-007; S-008; S-009;
S-010; S-011; S-012; S-013; S-014;
S-015; S-016; S-017; S-018; S-019;
S-020; S-021; S-022; S-023; S-024;
S-028**

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	X
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-084/S-001; S-002; S-003; S-004;
S-005; S-006; S-007; S-008; S-009;
S-010; S-011; S-012; S-013; S-014;
S-015; S-016; S-017; S-018; S-019;
S-020; S-021; S-022; S-023; S-024;
S-028**

APPROVAL LETTERS

DW

ANDA 40-084/S-001, S-002

Mallinckrodt Chemical, Inc.
Attention: Charles H. Smith
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

JUL 29 1996

Dear Sir:

This is in reference to your supplemental new drug applications dated June 3, 1995, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 mg/660 mg.

Reference is also made to your amendments dated May 31, 1996.

The supplemental applications provide for:

S-001: New tablet strength containing Hydrocodone Bitartrate 10 mg and Acetaminophen 660 mg.

S-002: Labeling Revision

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-084/S-003, S-004, S-005, S-006

Mallinckrodt Chemical, Inc.
Attention: Charles H. Smith
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

JUL 3 1996

Dear Sir:

This is in reference to your supplemental new drug applications dated July 25, 1995 (S-003, S-004) and September 1, 1995 (S-005, S-006) submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg.

Reference is also made to your amendments dated April 30, 1996 and May 29, 1996.

The supplemental applications provide for:

- S-003: Additional packaging configuration of 1000 tablets per bottle for the 7.5 mg/750 mg product.
- S-004: Labeling revision for 7.5 mg/750 mg product.
- S-005: New packaging configuration - 1000 count bottles of 5 mg/ 500 mg strength product.
- S-006: Labeling revision for 5 mg/500 mg product.

We have completed the review of these supplemental applications and they are approved.

**APPEARS THIS WAY
ON ORIGINAL**

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

92

ANDA 40-084/S-007, S-008

Mallinckrodt Chemical, Inc.
Attention: Charles H. Smith
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

OCT 16 1996



Dear Sir:

This is in reference to your supplemental new drug applications dated December 8, 1995, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg.

Reference is made to your amendments dated August 1, 19 and September 11, 1996.

The supplemental applications provide for:

- S-007: An additional product strength of Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/650 mg.
- S-008: Labeling Revision incorporating additional product strength.

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

DW

ANDA 40-084/S-009 (5 mg/500 mg, 7.5 mg/750 mg,
10 mg/660 mg and 10 mg/650 mg)
89-160/S-012 (5 mg/500 mg)
89-725/S-015 (7.5 mg/650 mg)

Mallinckrodt Chemical, Inc.
Attention: Marianne Robb
16305 Swingley Ridge Drive
Chesterfield, MO 63017

JUL 11 1997



Dear Madam:

This is in reference to your supplemental new drug applications dated November 26, 1996, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug applications for Hydrocodone Bitartrate and Acetaminophen Tablets, USP.

Reference is also made to your amendments dated May 22, 1997.

The supplemental applications provide for revised package insert labeling reflecting a combined insert for all three ANEXIA[®] product strengths (5 mg/500 mg, 7.5 mg/650 mg, and 10 mg/660 mg) and a combined insert for all five generic strengths (5 mg/500 mg, 7.5 mg/650 mg, 7.5 mg/750 mg, 10 mg/650 mg, 10 mg/660 mg).

We have completed the review of these supplemental applications and they are approved. However, at the time of next printing increase the print size of the molecular formula and the molecular weight in the DESCRIPTION section.

Revised insert labeling may be submitted in an annual report provided the changes are described in full. We refer you to 21 CFR 314.81(b)(2)(iii) for further guidance.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

APPEARS THIS WAY
ON ORIGINAL

The material submitted is being retained in our files.

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-084/S-009
89-160/S-012
89-725/S-015
Division File
HFD-92 with labeling
HFD-600/Reading File
HFD-610/JPhillips
Field Copy
njg/7/1/97/x:\...40084s9.apl
APPROVAL LETTER - MULTIPLE SUPPLEMENTS

Endorsements:
HFD-613/JWhite
HFD-613/CHoppes
HFD-613/JGrace

APPEARS THIS WAY
ON ORIGINAL

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

Florence S. Fang

3/13/2000

ff

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

40084 8016 14.1

See Attached

APR 11 2002

Mallinckrodt Inc.
Attention: Melissa Cay
675 McDonnell Blvd
St Louis, Missouri 63134

Dear Madam:

This is in reference to your supplemental new drug application dated November 30, 2001, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug applications noted on the attached list.

This supplemental application, submitted as "Changes Being Effected in 30 Days", provides for the following changes:

The addition of _____ as _____

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

U.V. Van der Staan

for Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Globals Attachment:

40-084/S-016: Hydrocodone Bitartrate/Acetaminophen
~~40-201/S-007~~: Hydrocodone Bitartrate/Acetaminophen
~~40-400/S-001~~: Hydrocodone Bitartrate/Acetaminophen
~~40-419/S-001~~: Acetaminophen/Codeine Phosphate
~~89-160/S-032~~: Acetaminophen/Hydrocodone Bitartrate
~~89-725/S-027~~: Acetaminophen/Hydrocodone Bitartrate

**APPEARS THIS WAY
ON ORIGINAL**

ANDA 40-084/S-017, S-018

DEC -2 2002

Mallinckrodt Inc.
Attention: Melissa Cay
675 McDonnell Blvd.
P.O. 5840
St. Louis, MO 63134-0840

Dear Madam:

This is in reference to your supplemental new drug applications dated January 11, 2002, submitted under 505(j) of Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 10 mg/650 mg and 10 mg/660 mg.

Reference is also made to your amendments dated: July 1, July 24, and August 26, 2002.

These supplemental applications, submitted as "Changes Being Effected in 30 days", provide for the following changes:

S-017: The addition of 30, 60, 90 and 120 count bottle sizes

S-018: New container labels

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

APPEARS THIS WAY
ON ORIGINAL

The material submitted is being retained in our files.

Sincerely yours,



4/27/02

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Mallinckrodt Inc.
Attention: Russell D. Reed
675 McDonnell Blvd
P.O. Box 5840
St. Louis, MO 63134-0840

APR 11 2010

Dear Sir:

This is in reference to your supplemental new drug application dated September 24, 2002, submitted pursuant to 21 CFR 314.70(c) "Special Supplement - Changes Being Effected" regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 10 mg/650 mg, 10 mg/660 mg and Anexsia® (Hydrocodone Bitartrate and Acetaminophen Tablets, USP) 10 mg/660 mg.

The supplemental application provides for revised package insert labeling reflecting changes requested in the Agency's letter dated July 3, 2002 regarding ANDA 40-468.

We have completed the review of this supplemental application and it is approved. However, we have the following comments:

1. CONTAINER

We note that you have proposed the proprietary name Anexsia® for your drug product, Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/660 mg. Since you are proposing the same proprietary name "Anexsia®" approved for your drug products of three different strengths, we ask that you print the following text in a prominent manner so that it may prevent potential medication errors due to the confusion of strengths:

Multiple strengths: Do not dispense unless strength is stated.

2. INSERT

- a. Regarding your proposed proprietary name, Anexsia®, please be reminded that the requirements for 21 CFR 201.10(g)(1) should be met. Please revise your insert labeling containing the proprietary name in this regard.

- b. We ask that you further revise your labeling as follows:

PRECAUTIONS - Include the following subsection as the last one in this section:

Geriatric Use - Clinical Studies of hydrocodone bitartrate and acetaminophen tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hydrocodone and the major metabolites of acetaminophen are known to be substantially excreted by the kidney. Thus the risk of toxic reactions may be greater in patients with impaired renal function due to the accumulation of the parent compound and/or metabolites in the plasma. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Hydrocodone may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of hydrocodone bitartrate and acetaminophen tablets and observed closely.

Please revise the container labels and insert labeling as instructed above and submit in final print as a "Special Supplement - Changes Being Effected" in accordance with 21 CFR 314.70(c) to this approved application.

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 with your last submission with all differences annotated and explained.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,



4/10/03

Wm Peter Rickman

Director

Division of Labeling and Program Support

Office of Generic Drugs

Center for Drug Evaluation and Research

cc: ANDA 40-084/S-020
Division File
HFD-92

V:\FIRMSAMMALLINCKRODT\LTRS&REV\40084s20AP.LABELING.doc

ENDORSEMENTS: HFD-613/CPARK
HFD-613/LGolson



Approval Letter - Single Supplement

FOR THE RECORD

The comments regarding PRECAUTIONS, Geriatric Use is based on the consult response from HFD-550 on 40-094/S-023 (Hydrocodone Bitartrate and APAP Tablets USP, 7.5 mg/650 mg, 10 mg/650 mg, & 10 mg/660 mg), received on 3/5/03. The sponsor withdrew S-023 and submitted a new supplement (S-024). These comments should be applicable to all Hydrocodone Bitartrate/APAP tablets, USP of different strengths.

APPEARS THIS WAY
ON ORIGINAL

ANDA 40-084/S-021

APR 25 2003

Mallinckrodt Inc.
Attention: Marianne Rob
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134-0840

Dear Madam:

This is in reference to your supplemental new drug application dated November 20, 2002, submitted under 505(j) of Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 10 mg/650 mg and 10 mg/660 mg.

This supplemental application, submitted as "Prior Approval" provides for the following change:

S-021: Provides for ~~the following change~~ as an in-process specification.

We have completed the review of this supplemental application, and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

for 

4/24/03

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-084/S-022

JUL 16 2003

Mallinckrodt Inc.
Attention: Russell D. Reed
675 McDonnell Blvd
P.O. Box 5840
St. Louis, MO 63134-0840

Dear Sir:

This is in reference to your supplemental new drug application dated June 26, 2003, submitted pursuant to 21 CFR 314.70(c) "Special Supplement - Changes Being Effected" regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 10 mg/650 mg, 10 mg/660 mg and Anexsia® (Hydrocodone Bitartrate and Acetaminophen Tablets, USP) 10 mg/660 mg.

The supplemental application provides for revised package insert labeling reflecting the addition of a "Geriatric Use" subsection in the PRECAUTIONS section. In addition, it provides for revised container labels for Anexsia® as requested in the Agency's letter of April 11, 2003.

We have completed the review of this supplemental application and it is approved. However, at the time of next printing, please revise the storage temperature statement on all labeling to read "Store at 20 to 25°C (68 to 77°F). [see USP Controlled Room Temperature]".

Revised labels and labeling may be submitted in an annual report provided all changes are described in full.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,



Wm Peter Rickman

Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

7/15/03

cc: ANDA 40-084/S-022
Division File
HFD-92

V:\FIRMSAM\MALLINCKRODT\LTRS&REV\40084s22AP.LABELING.doc

ENDORSEMENTS: HFD-613/CPARK
HFD-613/LGolson

CPark 7/16/03

Approval Letter - Single Supplement

FOR THE RECORD

The sponsor proposed separate package insert labeling for each strength and one using a proprietary name, Anexsia®. We find this proposal is acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

40084

18.1

NOV 13 2003

ANDAs: See Attached

5-023

Mallinckrodt, Inc.
Attention: Ms. Marianne Robb
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Dear Madam:

This is in reference to your supplemental new drug applications dated October 27, 2003, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug applications for drug products noted on the attached list.

These supplemental applications provide for _____ as an approved in-process control.

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,



11/13/03

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center of Drug Evaluation and Research

Attachment:

<u>ANDA No.</u>	<u>Drug Product Name</u>
40-201/S-014	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/500 mg and 10 mg/500 mg
89-725/S-035	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/650 mg
75-983/S-006	Tramadol Hydrochloride Tablets, 50 mg
74-184/S-005	Methadone Hydrochloride Tablets USP, 40 mg
40-084/S-023	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg
89-160/S-039	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg
40-436/S-001	Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg
40-419/S-007	Acetaminophen and Codeine Phosphate Tablets USP, 300 mg/15 mg, 300 mg/30 mg, and 300 mg/60 mg
40-352/S-002	Meperidine Hydrochloride Tablets USP, 50 mg and 100 mg
40-300/S-002	Methylphenidate Hydrochloride Tablets USP, 5 mg, 10 mg, and 20 mg
75-738/S-009	Propoxyphene Napsylate and Acetaminophen Tablets USP, 100 mg/650 mg
75-629/S-003	Methylphenidate Hydrochloride Extended-Release Tablets USP, 10 mg and 20 mg
40-050/S-007	Methadone Hydrochloride Tablets USP, 5 mg and 10 mg
40-405/S-009	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/325 mg
40-409/S-007	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/325 mg
40-400/S-007	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/325 mg

**APPEARS THIS WAY
ON ORIGINAL**

LF

40084

8024

v18.1

ANDA See attached(6)

Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Blvd.
P.O. 5840
St. Louis, MO 63134-0840

JUN - 1 2004

Dear Madam:

This is in reference to your supplemental new drug applications dated December 16, 2003, submitted under 505(j) of Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug applications for the drug products noted on the attached list.

These supplemental applications, submitted as "Prior Approval Supplements", provide for ~~_____~~

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for approved abbreviated new drug applications described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

R.C. Adams Jr

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-084/S-025, S-026

D.W

12/6/04

Mallinckrodt Inc.
Attention: Ronald Groman
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134-0840

Dear Sir:

This is in reference to your supplemental new drug applications dated June 9, 2004, submitted under 505(j) of Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg.

Reference is also made to your amendment dated July 30, 2004.

These supplemental applications, submitted as "Changes Being Effected-30 Days" provide for a new bulk packaging container/closure configuration(S-025) and new bulk container labeling (S-026).

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

40-084/S-001

ANDAs: See attached (32)

Mallinckrodt, Inc.
Attention: Ron Groman
675 McDonnell Blvd
P.O. Box 5840
St. Louis, MO 63134

Dear Sir:

This is in reference to your supplemental new drug applications dated June 30, 2004, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug applications listed on the attached pages.

These supplemental applications, submitted as "Supplement - Changes Being Effected in 30 days" provide for:

See attached: To add _____

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for the approved abbreviated new drug applications described in 21 CFR 314.80-81.

The materials submitted are being retained in our files.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment:

<u>ANDA No.</u>	<u>Drug Product Name</u>
40-050/S-007	Methadose Oral Tablets (Methadone Hydrochloride Tablets USP, 5 mg and 10 mg)
40-084/S-024	Hydrocodone Bitartrate and Acetaminophen Tablets USP, (7.5 mg/750 mg, 10 mg/650 mg and 10 mg/660 mg)
40-201/S-015	Hydrocodone Bitartrate and Acetaminophen Tablets USP, (7.5 mg/500 mg, 10 mg/500 mg)
74-184/S-006	Methadose Dispersible Tablets (Methadone Hydrochloride tablets USP, 40 mg)
89-160/S-040	ANEXIA Hydrocodone Bitartrate and Acetaminophen Tablets USP, (5 mg/500mg)
89-725/S-036	Hydrocodone Bitartrate and Acetaminophen Tablets USP, (7.5 mg/650 mg)

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-084/S-001; S-002; S-003; S-004;
S-005; S-006; S-007; S-008; S-009;
S-010; S-011; S-012; S-013; S-014;
S-015; S-016; S-017; S-018; S-019;
S-020; S-021; S-022; S-023; S-024;
S-028**

**TENTATIVE APPROVAL
LETTER**

/a

ANDA 40-084/S-009 (5 mg/500 mg, 7.5 mg/750 mg,
10 mg/660 mg and 10 mg/650 mg)
89-160/S-012 (5 mg/500 mg)
89-725/S-015 (7.5 mg/650 mg)

Mallinckrodt Chemical, Inc.
Attention: Marianne Robb
16305 Swingley Ridge Drive
Chesterfield, MO 63017

3 1997



Dear Madam:

This is in reference to your supplemental new drug applications dated November 26, 1996, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug applications for Hydrocodone Bitartrate and Acetaminophen Tablets, USP.

The supplemental applications provide for revised package insert labeling reflecting a combined insert for all three ANEXIA[®] product strengths (5 mg/500 mg, 7.5 mg/750 mg, and 10 mg/660 mg) and a combined insert for all five generic strengths (5 mg/500 mg, 7.5 mg/650 mg, 7.5 mg/750 mg, 10 mg/650 mg, 10 mg/660 mg).

We have completed the review of these supplemental applications and they are approvable. However, before the supplemental applications may be approved, it is necessary that you prepare and submit final printed insert labeling as amendments to these supplemental applications.

The changes provided for in these supplemental applications may not be initiated until you have been notified in writing that the supplemental applications are approved.

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-084/S-001; S-002; S-003; S-004;
S-005; S-006; S-007; S-008; S-009;
S-010; S-011; S-012; S-013; S-014;
S-015; S-016; S-017; S-018; S-019;
S-020; S-021; S-022; S-023; S-024;
S-028**

FINAL PRINTED LABELING

931774



ANEXSIA® 10/660

Hydrocodone Bitartrate*
and Acetaminophen
Tablets, USP

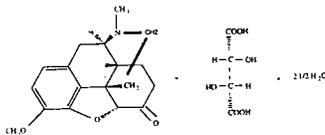


*Warning: May be habit forming.

DESCRIPTION

ANEXSIA® 10/660 (hydrocodone bitartrate and acetaminophen) are supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5 α -epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{19}H_{21}NO_4 \cdot C_4H_4O_6 \cdot 1 1/2 H_2O$

MW = 464.50

Acetaminophen, 4-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$

MW = 151.17

Each ANEXSIA® 10/660 tablet contains:

Hydrocodone Bitartrate*, USP 10 mg
 *(Warning: May be habit forming)
 Acetaminophen, USP 660 mg

In addition each ANEXSIA® 10/660 tablet contains the following inactive ingredients: Magnesium Stearate NF, Pregelatinized Starch NF, Starch (corn) NF, and Stearic Acid NF.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α - and 6- β -hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, ANEXSIA® 10/660 tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when ANEXSIA® 10/660 tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with ANEXSIA® 10/660 tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. ANEXSIA® 10/660 tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: ANEXSIA® 10/660 Tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP) are classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when ANEXSIA® 10/660 tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdose, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdose, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

ANEXSIA® 10/660: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

HOW SUPPLIED

Each ANEXSIA® 10/660 tablet contains Hydrocodone Bitartrate® 10 mg (Warning: May be habit forming) and Acetaminophen 660 mg. It is available as a white, capsule shaped, bisected tablet debossed with a KPI 3 identification number.

Bottles of 100 NDC No. 0406-5363-01

Bottles of 1000 NDC No. 0406-5363-10

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

A Schedule III Narcotic.

Federal (U.S.A.) law prohibits dispensing without prescription.

ANEXSIA® is a registered trademark of Mallinckrodt Chemical, Inc.

Manufactured for
Mallinckrodt Chemical, Inc.
Chesterfield, Missouri 63017, U.S.A.

**MALLINCKRODT
CHEMICAL**



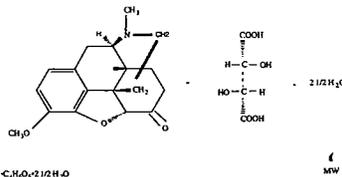
**HYDROCODONE BITARTRATE*
AND ACETAMINOPHEN
TABLETS, USP** 
5/500 and 7.5/750

*Warning: May be habit forming.

DESCRIPTION

Hydrocodone Bitartrate and Acetaminophen Tablets are supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 5/500 tablet contains:
Hydrocodone Bitartrate, USP..... 5 mg
(Warning: May be habit forming)
Acetaminophen, USP..... 500 mg

In addition each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 5/500 tablet contains the following inactive ingredients: Magnesium Stearate NF, Pregelatinized Starch NF, (Corn) Starch NF, Stearic Acid NF and Purified Water USP.

Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 7.5/750 tablet contains:
Hydrocodone Bitartrate, USP..... 7.5 mg
(Warning: May be habit forming)
Acetaminophen, USP..... 750 mg

In addition each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 7.5/750 tablet contains the following inactive ingredients: Magnesium Stearate NF, Pregelatinized Starch NF, (Corn) Starch NF, Stearic Acid NF and Purified Water USP.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, hydrocodone bitartrate and acetaminophen tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when hydrocodone bitartrate and acetaminophen tablets are used post-operatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Tablets are classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdose, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdose, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids.

Nasopharynx and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSEAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 5/500: The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 7.5/750: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 5 tablets.

HOW SUPPLIED

Each HYDROCODONE BITARTRATE AND ACETAMINOPHEN, USP 5/500 tablet contains Hydrocodone Bitartrate 5 mg (Warning: May be habit forming) and Acetaminophen 500 mg. It is available as a white, round bisected tablet debossed with a KPI 12 identification number.

Bottles of 100..... NDC No. 0406-0358-01
Bottles of 1000..... NDC No. 0406-0358-10

Each HYDROCODONE BITARTRATE AND ACETAMINOPHEN, USP 7.5/750 tablet contains Hydrocodone Bitartrate 7.5 mg (Warning: May be habit forming) and Acetaminophen 750 mg. It is available as a white, round bisected tablet debossed with a KPI 2 identification number.

Bottles of 100..... NDC No. 0406-0360-01
Bottles of 1000..... NDC No. 0406-0360-10

Dispense in a tight, light-resistant container as defined in USP Storage: Store at controlled room temperature 15° to 30°C (59° to 86°F).
A Schedule III Narcotic.

Federal (U.S.A.) law prohibits dispensing without prescription.

Manufactured for
Mallinckrodt Chemical, Inc.
Chesterfield, Missouri 63017, U.S.A.

**MALLINCKRODT
CHEMICAL**

SAMPLE



**HYDROCODONE BITARTRATE* AND
ACETAMINOPHEN TABLETS, USP**
10 mg/650 mg

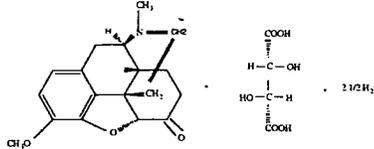


*Warning: May be habit forming.

SPECIMEN

Hydrocodone Bitartrate and Acetaminophen Tablets are supplied in tablet form for oral administration.

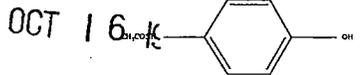
Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2.5). It has the following structural formula:



$C_{28}H_{35}NO_7 \cdot C_4H_4O_6 \cdot 2 \frac{1}{2} H_2O$

MW = 494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_9H_9NO_2$

MW = 151.17

Each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 10 mg/650 mg tablet contains:
Hydrocodone Bitartrate, USP..... 10 mg
*Warning: May be habit forming)

Acetaminophen, USP..... 650 mg
In addition each HYDROCODONE BITARTRATE* AND ACETAMINOPHEN, USP 10 mg/650 mg tablet contains the following inactive ingredients: Magnesium Stearate NF, Pregelatinized Starch NF, (Corn) Starch NF, Stearic Acid NF.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the blockade of opiate receptors in the central nervous system. In addition to analgesic and antitussive effects, opiates produce drowsiness, changes in mood and mental clouding.

The analgesic action of Acetaminophen is of a peripheral influence, but the specific mechanism is as yet undetermined. Its pyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.
Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

See OVERDOSAGE for toxicity information.
Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdose. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, hydrocodone bitartrate and acetaminophen tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when hydrocodone bitartrate and acetaminophen tablets are used post-operatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving narcotics, anticholinergics, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Tablets are classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 10 mg/650 mg: The usual adult dosage is one tablet every four to six hours as needed for pain. The total 24 hour dosage should not exceed 6 tablets.

HOW SUPPLIED

Each **HYDROCODONE BITARTRATE AND ACETAMINOPHEN, USP 10 mg/650 mg** tablet contains Hydrocodone Bitartrate 10 mg (Warning: May be habit forming) and Acetaminophen 650 mg. It is available as a blue, capsule shaped tablet, scored with a KPI 10 identification number.

Bottles of 100.....NDC No. 0406-0361-01
Bottles of 1000.....NDC No. 0406-0361-10

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

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

A Schedule III Narcotic.

Federal (U.S.A.) law prohibits dispensing without prescription.

Manufactured by King Pharmaceuticals, Inc., Bristol, TN 37620, U.S.A.

Manufactured for
Mallinckrodt Chemical, Inc.
Chesterfield, Missouri 63017, U.S.A.



HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
10 mg/650 mg

FINAL PRINTED LABELING

Sample 3's

SPECIMEN

NDC 0406-0361-03

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP

Each tablet contains:
Hydrocodone Bitartrate, USP 10 mg
Acetaminophen, USP 650 mg

WARNING: May be habit forming.

3 TABLETS - PROFESSIONAL SAMPLE
KEEP OUT OF REACH OF CHILDREN

MALLINCKRODT CHEMICAL

USUAL DOSAGE: See package insert. Federal (USA) law prohibits dispensing without prescription.

Each tablet contains a controlled substance as defined by 21 CFR 314.101. Dispense in a unit-of-use container as defined in 21 CFR 314.105. For information, contact Mallinckrodt Chemical, Inc., 7000 North Pleasant Street, St. Louis, MO 63130, or Mallinckrodt Chemical, Inc., 81901, TN 37120.

PROFESSIONAL SAMPLE - NOT TO BE SOLD

3 0406-0361-03 4
022415



APPROVED

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
10 mg/650 mg

FINAL PRINTED LABELING

100's

SPECIMEN

NDC 0406-0361-01

0406-0361-01 0 032416

HYDROCODONE BITARTRATE* AND ACETAMINOPHEN
TABLETS, USP
10 mg/650 mg

Each tablet contains:
Hydrocodone Bitartrate*, USP 10 mg
*WARNING: May be habit forming.
Acetaminophen, USP 650 mg
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

100 TABLETS

MALLINCKRODT CHEMICAL

USUAL DOSAGE:
See package insert for complete dosage recommendations.

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

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

Manufactured for Mallinckrodt Chemical, Inc. Chesterfield, Missouri 63017, U.S.A. by King Pharmaceuticals, Inc. Bristol, TN 37620, U.S.A.

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
10 mg/650 mg

FINAL PRINTED LABELING

1000's

NDC 0406-0361-10

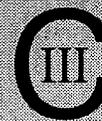
DOT 15 1996

SPECIMEN



032418

**HYDROCODONE
BITARTRATE[®]
AND ACETAMINOPHEN**



TABLETS, USP

10 mg/650 mg

Each tablet contains:
Hydrocodone Bitartrate[®], USP 10 mg
***WARNING:** May be habit forming.
Acetaminophen, USP 650 mg
CAUTION: Federal (U.S.A.) law prohibits
dispensing without prescription.

1000 TABLETS

**MALLINCKRODT
CHEMICAL**

APPROVED

USUAL DOSAGE:
See package insert for
complete dosage
recommendations.

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

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

Manufactured for
Mallinckrodt Chemical, Inc.
Chesterfield, Missouri 63017,
U.S.A.
by
King Pharmaceuticals, Inc.
Bristol, TN 37620, U.S.A.



03600502



HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 7.5 mg/750 mg Rx only

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP

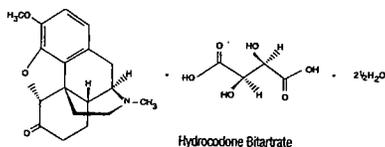
7.5 mg/750 mg
Rx only



DESCRIPTION

Hydrocodone Bitartrate and Acetaminophen Tablets are supplied in tablet form for oral administration. Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is: 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2.5). It has the following structural formula:

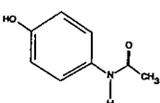
APPROVED
APR 11 2001



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

MW=494.490

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_9H_9NO_2$

MW = 151.16

SPECIMEN

Each HYDROCODONE BITARTRATE AND ACETAMINOPHEN, USP 7.5 mg/750 mg tablet contains:

Hydrocodone Bitartrate, USP.....7.5 mg
Acetaminophen, USP.....750 mg

In addition, each HYDROCODONE BITARTRATE AND ACETAMINOPHEN, USP 7.5 mg/750 mg tablet contains the following inactive ingredients: Crospovidone NF, Magnesium Stearate NF, Microcrystalline Cellulose NF, Povidone USP, Pregelatinized Starch NF, Silicon Dioxide NF, and Stearic Acid NF. Meets USP Dissolution Test 1.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites. See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdose. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug. See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen. Patients known to be hypersensitive to other opioids may exhibit cross-sensitivity to hydrocodone.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, hydrocodone bitartrate and acetaminophen tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when hydrocodone bitartrate and acetaminophen tablets are used post-operatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.



03600502



HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 7.5 mg/750 mg Rx only

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:
Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are fight-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

- Central Nervous System:** Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.
- Gastrointestinal System:** Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.
- Genitourinary System:** Urteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.
- Respiratory Depression:** Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory centers (see OVERDOSAGE).
- Special Senses:** Cases of hearing impairment or permanent loss have been reported predominantly in patients with chronic overdose.
- Dermatological:** Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis. Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Tablets are classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdose, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdose: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 grams.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 7.5 mg/750 mg: The usual adult dosage is one tablet every four to six hours as needed for pain. The total 24-hour dosage should not exceed 5 tablets.

HOW SUPPLIED

Each HYDROCODONE BITARTRATE AND ACETAMINOPHEN, USP 7.5 mg/750 mg tablet contains Hydrocodone Bitartrate 7.5 mg and Acetaminophen 750 mg. It is available as a white, capsule-shaped tablet debossed with an M360 on one side and bisected on the other side.

Bottles of 30	NDC No. 0406-0360-03
Bottles of 60	NDC No. 0406-0360-06
Bottles of 90	NDC No. 0406-0360-09
Bottles of 100	NDC No. 0406-0360-01
Bottles of 120	NDC No. 0406-0360-12
Bottles of 500	NDC No. 0406-0360-05
Unit Dose (10x10)	NDC No. 0406-0360-62

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

Storage: Store at controlled room temperature 15° to 30°C (59° to 86°F) [see USP]. Protect from light. A Schedule III Narcotic.

Mallinckrodt Inc.
St. Louis, Missouri 63134, U.S.A.
MG #15164

tyco

Healthcare

Mallinckrodt

Rev 051702

MALLINCKRODT

NDC 0406-0360-63

100 TABLETS (4X25)-Unit Dose

USUAL DOSAGE:
See package insert
for complete dosage
recommendations.

STORAGE: Store at
controlled room
temperature 15° to 30°C
(59° to 86°F). Keep
tablets in box to
protect from light.

This unit-dose
package is not child
resistant.

SPECIMEN

**HYDROCODONE BITARTRATE AND
ACETAMINOPHEN TABLETS, USP**

7.5 mg/750 mg

Rx only

Exp. Date:

Lot No.:



**HYDROCODONE BITARTRATE AND
ACETAMINOPHEN TABLETS, USP**

7.5 mg/750 mg

Rx only

100 TABLETS (4X25)-Unit Dose

NDC 0406-0360-63

100 TABLETS

MALLINCKRODT

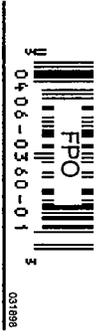
Mallinckrodt Inc.
St. Louis, MO 63134

Each tablet contains:
Hydrocodone Bitartrate, USP 7.5 mg
Acetaminophen, USP 750 mg

FINAL PRINTED LABELING
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
(7.5 mg/750 mg)
CONTAINER LABEL (100s)

NDC 0406-0360-01

SPECIMEN



0406-0360-01

FPO

8861830

HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP

7.5 mg/750 mg

Each tablet contains:
Hydrocodone Bitartrate, USP 7.5 mg
Acetaminophen, USP 750 mg
Rx only

100 TABLETS

MALLINCKRODT

USUAL DOSAGE:
See package insert for complete dosage recommendations.

STORAGE: Store in a controlled room at a temperature 15° to 30°C (59° to 86°F). Protect from light.

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

Mallinckrodt Inc.
St. Louis, Missouri
63134, U.S.A.

REMOVED

MAR 13 2000

FINAL PRINTED LABELING
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
(7.5 mg/750 mg)
CONTAINER LABEL (500s)

NDC 0406-0360-05

SPECIMEN



HYDROCODONE 
BITARTRATE
AND ACETAMINOPHEN
TABLETS, USP

7.5 mg/750 mg

Each tablet contains:
Hydrocodone Bitartrate, USP 7.5 mg
Acetaminophen, USP
Rx only

500 TABLETS

MALLINCKRODT

APPROVED

MAR 13 2000

USUAL DOSAGE:
See package insert for
complete dosage
recommendations.

STORAGE: Store at controlled
room temperature 15° to 30°C
(59° to 86°F). Protect from light.

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

Mallinckrodt Inc.
St. Louis, Missouri
63134, U.S.A.

FINAL PRINTED LABELING
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
(7.5 mg/750 mg)
UNIT DOSE LABEL

Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 1	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 2	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 3	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 4	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 5
SPECIMEN				
Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 6	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 7	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 8	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 9	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 10
Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 11	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 12	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 13	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 14	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 15
Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 16	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 17	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 18	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 19	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 20
Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 21	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 22	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 23	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 24	Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg MALLINCKRODT INC. ST. LOUIS, MO 63134 25

SPECIMEN



N 0406-5363-01 9 0831770

NDC 0406-5363-01

ANEXSIA[®] 10/660
HYDROCODONE BITARTRATE
AND ACETAMINOPHEN
TABLETS, USP



Each tablet contains:
Hydrocodone Bitartrate*, USP 10 mg
*WARNING: May be habit forming.
Acetaminophen, USP 660 mg
CAUTION: Federal (U.S.A.) law prohibits
dispensing without prescription.

100 TABLETS

MALLINCKRODT
CHEMICAL

29 1998

USUAL DOSAGE:
See package insert
for complete dosage
recommendations.

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

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

Manufactured for
Mallinckrodt Chemical, Inc.
Chesterfield, Missouri
63017, U.S.A.

APPROVED

SPECIMEN



N 0406-5363-01 9 0831770

NDC 0406-5363-01

ANEXSIA[®] 10/660
HYDROCODONE BITARTRATE
AND ACETAMINOPHEN
TABLETS, USP



Each tablet contains:
Hydrocodone Bitartrate*, USP 10 mg
*WARNING: May be habit forming.
Acetaminophen, USP 660 mg
CAUTION: Federal (U.S.A.) law prohibits
dispensing without prescription.

100 TABLETS

MALLINCKRODT
CHEMICAL

29 1998

USUAL DOSAGE:
See package insert
for complete dosage
recommendations.

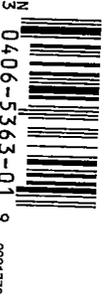
STORAGE: Store
at controlled room
temperature 15° to 30°C
(59° to 86°F).

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

Manufactured for
Mallinckrodt Chemical, Inc.
Chesterfield, Missouri
63017, U.S.A.

APPROVED

SPECIMEN



N 0406-5363-01 9 0831770

NDC 0406-5363-01

ANEXSIA[®] 10/660
HYDROCODONE BITARTRATE
AND ACETAMINOPHEN
TABLETS, USP



Each tablet contains:
Hydrocodone Bitartrate*, USP 10 mg
*WARNING: May be habit forming.
Acetaminophen, USP 660 mg
CAUTION: Federal (U.S.A.) law prohibits
dispensing without prescription.

100 TABLETS

MALLINCKRODT
CHEMICAL

29 1998

USUAL DOSAGE:
See package insert
for complete dosage
recommendations.

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

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

Manufactured for
Mallinckrodt Chemical, Inc.
Chesterfield, Missouri
63017, U.S.A.

APPROVED

SPECIMEN



N 0406-5363-01 9 0831770

NDC 0406-5363-01

ANEXSIA[®] 10/660
HYDROCODONE BITARTRATE
AND ACETAMINOPHEN
TABLETS, USP



Each tablet contains:
Hydrocodone Bitartrate*, USP 10 mg
*WARNING: May be habit forming.
Acetaminophen, USP 660 mg
CAUTION: Federal (U.S.A.) law prohibits
dispensing without prescription.

100 TABLETS

MALLINCKRODT
CHEMICAL

29 1998

USUAL DOSAGE:
See package insert
for complete dosage
recommendations.

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

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

Manufactured for
Mallinckrodt Chemical, Inc.
Chesterfield, Missouri
63017, U.S.A.

APPROVED

NDC 0406-5363-10

SPECIMEN



0981772

ANEXSIA® 10/660
HYDROCODONE BITARTRATE*
AND ACETAMINOPHEN
TABLETS, USP

Each tablet contains:
 Hydrocodone Bitartrate*, USP 10 mg
 ***WARNING:** May be habit forming.
 Acetaminophen, USP 660 mg
CAUTION: Federal (U.S.A.) law prohibits
 dispensing without prescription.

1000 TABLETS



JUL 29 1996

USUAL DOSAGE:
See package insert for complete dosage recommendations.

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

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

Manufactured for Mallinckrodt Chemical, Inc. Chesterfield, Missouri 63017, U.S.A.

MALLINCKRODT
CHE

APPROVED

NDC 0406-5363-10

SPECIMEN



0981772

ANEXSIA® 10/660
HYDROCODONE BITARTRATE*
AND ACETAMINOPHEN
TABLETS, USP

Each tablet contains:
 Hydrocodone Bitartrate*, USP 10 mg
 ***WARNING:** May be habit forming.
 Acetaminophen, USP 660 mg
CAUTION: Federal (U.S.A.) law prohibits
 dispensing without prescription.

1000 TABLETS



JUL 29 1996

USUAL DOSAGE:
See package insert for complete dosage recommendations.

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

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

Manufactured for Mallinckrodt Chemical, Inc. Chesterfield, Missouri 63017, U.S.A.

MALLINCKRODT
CHEMICAL

APPROVED

NDC 0406-5363-10

SPECIMEN



0981772

ANEXSIA® 10/660
HYDROCODONE BITARTRATE*
AND ACETAMINOPHEN
TABLETS, USP

Each tablet contains:
 Hydrocodone Bitartrate*, USP 10 mg
 ***WARNING:** May be habit forming.
 Acetaminophen, USP 660 mg
CAUTION: Federal (U.S.A.) law prohibits
 dispensing without prescription.

1000 TABLETS



JUL 29 1996

USUAL DOSAGE:
See package insert for complete dosage recommendations.

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

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

Manufactured for Mallinckrodt Chemical, Inc. Chesterfield, Missouri 63017, U.S.A.

MALLINCKRODT
CHEMICAL

APPROVED

NDC 0406-0360-10

HYDROCODONE BITARTRATE* AND ACETAMINOPHEN



TABLETS, USP

7.5 mg/750 mg

Each tablet contains:
Hydrocodone Bitartrate*, USP 7.5 mg

*WARNING: May be habit forming.
Acetaminophen, USP 750 mg

CAUTION: Federal (U.S.A.) law prohibits
dispensing without prescription.

1000 TABLETS

APPROVED

MALLINCKRODT
CHEMICAL

USUAL DOSAGE:

See package insert for complete dosage recommendations.

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

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

Manufactured for
Mallinckrodt Chemical, Inc.
Chesterfield, Missouri 63017,
U.S.A.



N
3 0406-0360-10 5

031596

JUL 3 1985



ANEXSIA® 5/500
ANEXSIA® 7.5/650
ANEXSIA® 10/660
 Hydrocodone Bitartrate*
 and Acetaminophen
 Tablets, USP

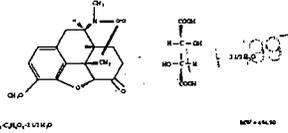


*Warning: May be habit forming

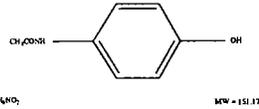
DESCRIPTION

ANEXSIA® Tablets (hydrocodone bitartrate and acetaminophen) are supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opiate analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5 α -epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2.5). It has the following structural formula:



Acetaminophen, 4-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



- Each ANEXSIA® 5/500 tablet contains:
- Hydrocodone Bitartrate*, USP 5 mg
 - *(Warning: May be habit forming)
 - Acetaminophen, USP 500 mg
- In addition, each ANEXSIA® 5/500 tablet contains the following inactive ingredients: Magnesium Stearate NF, Pregelatinized Starch NF, Starch (Corn) NF, and Stearic Acid NF.
- Each ANEXSIA® 7.5/650 tablet contains:
- Hydrocodone Bitartrate*, USP 7.5 mg
 - *(Warning: May be habit forming)
 - Acetaminophen, USP 650 mg
- In addition, each ANEXSIA® 7.5/650 tablet contains the following inactive ingredients: Magnesium Stearate NF, Pregelatinized Starch NF, Starch (Corn) NF, and Stearic Acid NF.
- Each ANEXSIA® 10/660 tablet contains:
- Hydrocodone Bitartrate*, USP 10 mg
 - *(Warning: May be habit forming)
 - Acetaminophen, USP 660 mg
- In addition, each ANEXSIA® 10/660 tablet contains the following inactive ingredients: Magnesium Stearate NF, Pregelatinized Starch NF, Starch (Corn) NF, and Stearic Acid NF.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 \pm 5.2 ng/mL. Maximum serum levels were achieved at 1.3 \pm 0.3 hours and the half-life was determined to be 3.8 \pm 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α - and 6- β -hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdose. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, ANEXSIA® tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when ANEXSIA® tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with this combination product and should be avoided.

Hydrocodone may be habit forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics,

Magnesium Stearate NF, Pregelatinized Starch NF, Starch (Corn) NF, and Stearic Acid NF.

Each ANEXSIA® 10/660 tablet contains:

Hydrocodone Bitartrate, USP 10 mg

(Warning: May be habit forming)

Acetaminophen, USP 660 mg

In addition, each ANEXSIA® 10/660 tablet contains the following inactive ingredients: Magnesium Stearate NF, Pregelatinized Starch NF, Starch (Corn) NF, and Stearic Acid NF.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α - and 6- β -hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdose. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, ANEXSIA® tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when ANEXSIA® tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with this combination product and should be avoided.

Hydrocodone may be habit forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with ANEXSIA® tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. ANEXSIA® tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-084/S-001; S-002; S-003; S-004;
S-005; S-006; S-007; S-008; S-009;
S-010; S-011; S-012; S-013; S-014;
S-015; S-016; S-017; S-018; S-019;
S-020; S-021; S-022; S-023; S-024;
S-028**

CSO LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING # 1

Supplement (FPL)

DATE OF REVIEW: September 24, 2004

ANDA: 40-084/S-026

NAME OF FIRM: Mallinckrodt, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg

DATE OF SUBMISSION: June 9, 2004

COMMENTS

CONTAINER - 5000s (Bulk Package)

The final printed labels submitted on June 9, 2004 appear acceptable.

RECOMMENDATIONS:

From the viewpoint of the labeling, this supplement may be approved.

FOR THE RECORD:

1. This CBE-30 days supplement was submitted in conjunction with the chemistry for a new bulk packaging container/closure system along with revised labels for the bulk package.
2. The review was done using the previously approved container labels.
3. Stability data has been provided for the bulk container exhibit batch for the 6 months expiration.
4. Since the labels submitted do not appear to be shipping labels, and the bulk packaging could be transferred to a hospital or other medical institutions for repackaging, we decided to review the labels for approval.

cc: ANDA 40-084/S-026
Dup/Division File
9/23/04 HFD-613/CPark/LGolson (no cc)

Far 9/29/04
J.W. Dolan 9/29/04

V:\FIRMSAMMALLINCKRODTLTRS&REV40084S26.AP.LABELING.doc
Review

REVIEW OF PROFESSIONAL LABELING # 1

Supplement (Draft)

DATE OF REVIEW: January 17, 2002

ANDA #: 40-084/S-018

NAME OF FIRM: Mallinckrodt Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, 10 mg/660 mg)

DATE OF SUBMISSION: January 14, 2002

COMMENTS

1. CONTAINER - 30s, 60s, 90s & 120s

We note that the expression of strength, 10 mg/660 mg is not sufficiently prominent due to lack of background contrast. We ask that you increase the prominence by changing the background color and/or by any other means.

2. INSERT

a. GENERAL

Although computer generated container and carton labeling is regarded acceptable as final print, it is required that you submit insert labeling in final print, not in photocopies to be acceptable. In addition, the insert labeling should be presented in one-piece, not in two-pieces as you have submitted.

b. DESCRIPTION

We encourage that you relocate the statement "Meet USP Dissolution Test 1" to appear in this section.

c. HOW SUPPLIED

See comment under DESCRIPTION.

Please revise the labels and labeling as directed above, then prepare and submit in final print as an amendment to this supplement.

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 with your last submission with all differences annotated and explained.

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Please verify that the statement "Meet USP Dissolution Test 1" is accurate.

*14/1
Parker in*

FOR THE RECORD:

1. This supplement was submitted in conjunction with chemistry for the new package sizes of 30s, 60s, 90s & 120s.
2. The review was done based on the last approved sponsor's labeling for these products.
3. The sponsor proposed Child-resistant cap to be in compliance with the Poison Prevention Acts for the sizes of 30s & 60s. (vol B. p.169)
4. The following-email was sent to Don on 1/17/02.

I note that this application was approved for 4 different strengths, 500 mg/5 mg, 650 mg/10 mg, 660 mg/10 mg, & 750 mg/7.5 mg. The 650 mg/10 mg strength was approved October 16, 1996 (S-007 & -008). However, this new strength is not listed in the O.B. I would like to bring this to your attention. Thanks,

5. The following is the response from Don on 1/17/02.

Gladys:

I am faxing you the 40-084 S-008 as a source document so that it may be added to the Orange Book. Don

cc:

ANDA 40-084/S-018

Dup/Division File

HFD-613/Cpark/CHoppes/(no cc:)

V:\FIRMSAM\MALLINCKRODT\LTRS&REV\40084s18AE.LABELING.doc

Review

Cham 1/22/02

[Signature] 1/23/02

REVIEW OF PROFESSIONAL LABELING # 2

Supplement (FPL)

DATE OF REVIEW: September 30, 2002

ANDA #: 40-084/S-018

NAME OF FIRM: Mallinckrodt Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, & 10 mg/660 mg)

DATE OF SUBMISSION: July 1, July 24, and August 26, 2002

COMMENTS

1. CONTAINER - 30s, 60s, 90s & 120s

Satisfactory in FPL as of **7/1/02** submission (vol. 15.1, "Final Printed Labeling" section)

2. INSERT

Satisfactory in FPL as of **7/1/02** submission for 7.5 mg/750 mg (Rev. 041902; Code# - MG #15164; vol. 15.1).

Satisfactory in FPL as of **7/24/02** submission for 10 mg/650 mg (Rev. 042002H; Code# - MG#15166; vol. 15.1)

Satisfactory in FPL as of **8/26/02** submission for 10 mg/660 mg (Rev. 042102; Code# - MG#15167, vol. 15.1)

FOR THE RECORD:

1. This supplement was submitted in conjunction with chemistry for the new package sizes of 30s, 60s, 90s & 120s.
2. The review was done based on the last approved sponsor's labeling for these products.
3. The sponsor proposed separate insert labeling for each strength. We find this acceptable.
4. The sponsor proposed Child-resistant cap to be in compliance with the Poison Prevention Acts for the sizes of 30s & 60s. (vol B. p.169)
5. The following-email was sent to Don on 1/17/02.

I note that this application was approved for 4 different strengths, 500 mg/5 mg, 650 mg/10 mg, 660 mg/10 mg, & 750 mg/7.5 mg. The 650 mg/10 mg strength was approved October 16, 1996 (S-007 & -008). However, this new strength is not listed in the O.B. I would like to bring this to your attention. Thanks,

6. The following is the response from Don on 1/17/02.

Gladys:

I am faxing you the 40-084 S-008 as a source document so that it may be added to the Orange Book. Don

7. The labeling should be revised as follows. This instruction was forwarded to the sponsor at the time of forwarding the labeling deficiency for unapproved ANDA 40-468 on July 3, 2002. The firm submitted this amendment on July 1, 2002, prior to the receipt of the 40-468 labeling deficiency letter and consequently did not revise the labeling accordingly in this supplement. Since this supplement is for the new package sizes and there is no pending chemistry issue, we will approve this supplement. I called Melissa Cay on July 23, 2002 and requested that once this supplement is approved, then the sponsor should send in a revised labeling including the following changes as a SSCBE. She stated that they intend to do as directed.

a. CONTRAINDICATIONS - Include the following text as the second paragraph:

Patients known to be hypersensitive to other opioids may exhibit cross-sensitivity to hydrocodone.

b. ADVERSE REACTIONS - Add the following text immediately following the "Respiratory Depression" subsection:

Special Senses: Cases of hearing impairment or permanent loss have been reported predominantly in patients with chronic overdose.

cc: ANDA 40-084/S-018
Dup/Division File
HFD-613/Cpark/LGolson (no cc)

C Park 10/1/02
JL Golson 10/1/02

V:\FIRMSAM\MALLINCKRODT\LTRS&REV\40084s18AP.LABELING.doc

Review

**APPEARS THIS WAY
ON ORIGINAL**

REVIEW OF PROFESSIONAL LABELING # 1

Supplement (Draft)

DATE OF REVIEW: December 17, 1998

ANDA #: 40-084/S-015

NAME OF FIRM: Mallinckrodt, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets,
USP (7.5 mg/750 mg, 10 mg/650 mg, & 10 mg/660 mg)

DATE OF SUBMISSION: June 30, 1998 and September 29, 1998
(Original supplement and amendment)

COMMENTS

1. Container - 100s & 500s

- a. We encourage you to increase the prominence of "Rx only".
- b. We encourage the inclusion of the statement "Protect from light."

2. Unit dose blister

Satisfactory in draft

3. Unit dose carton - 100s

The statement "Hydrocodone Bitartrate and Acetaminophen Tablets, USP ___ mg/___ mg" on the side panel should be replaced with "Each tablet contains:... " as found on the container labels.

4. Insert labeling

a. TITLE

We encourage the inclusion of "Rx only" underneath the TITLE.

b. HOW SUPPLIED

- i. We encourage the inclusion of the statement "Protect from light."
- ii. We encourage the relocation of "Rx only" to the

REVIEW OF PROFESSIONAL LABELING # 2

Amendment to Supplement (FPL)

DATE OF REVIEW: June 9, 1999

ANDA #: 40-084/S-015

NAME OF FIRM: Mallinckrodt, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets,
USP (7.5 mg/750 mg, 10 mg/650 mg, & 10 mg/660 mg)

DATE OF SUBMISSION: May 28, 1999

COMMENTS

From a labeling standpoint, the labels and labeling have been satisfactorily revised to reflect a new manufacturer.

RECOMMENDATIONS:

Inform the firm of the above comments.

FOR THE RECORD:

1. Review based on the labeling of the last approved labeling of this product of this firm. The labeling of the RLD has not been revised since the last approval of this firm's labeling.
2. This supplement was submitted in association with chemistry for a new manufacturer, formulation, manufacturing process, equipment, controls, container/closure system, packaging and labeling.
3. The firm has amended above referenced supplement to correct one of the inactive ingredients described erroneously in the original supplement. [e.g., , to Silicon Dioxide NF \square]
4. The inactive ingredients description is accurate. See p.211 of vol.8.1 & p.175 of vol.9.1.
5. The description of the products in the H.S section is accurate. (See p.1567, vol.8.4; p.1604, vol.8.4; p.1644, vol.8.4)
6. The firm has proposed separate package insert labeling for each strength as in the past.

7. CONTAINER/CLOSURE

Container: HDPE

Closure: Non-CRC

(See p.1370, vol.8.4)

cc: ANDA 40-084/S-015

Dup/Division File

HFD-613/AVeZZa/CHoppes / (no cc:)

aev/6/9/99|V:\FIRMSAM\MALLINK\LTRS&REV\40084S15.AEL

Review

**APPEARS THIS WAY
ON ORIGINAL**

D.V.

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

Date of Review: 2-15-96 Date of Submission: 9-1-95

Primary Reviewer: Adolph Vezza

Secondary Reviewer:

ANDA Number: 40-084/S-006 Review Cycle: FIRST

Applicant's Name [as seen on 356(h)]: King Pharmaceuticals, Inc.

Manufacturer's Name (If different than applicant): applicant

Proprietary Name:

Established Name: Hydrocodone Bitartrate and Acetaminophen
Tablets USP, 5 mg/500 mg

**LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE
CHEMISTRY COMMENTS TO THE FIRM:**

[NOTE: These deficiencies can be located on the x-drive as
detailed in notes from Ted Sherwood regarding the New X-Drive]

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

1. CONTAINER: 1000s

- a. Place an asterisk after the word "BITARTRATE" in the established name.
- b. Delete the "(Warning:...)" statement after the established name.
- c. Place an asterisk immediately before the "(Warning:...)" statement in the "Each Tablet..." statement. [i.e. *(Warning:...)]

2. INSERT

a. GENERAL COMMENT

Place the asterisk before the parenthesis in the

"Warning..." statement [*(Warning...)].

b. DESCRIPTION

Revise the molecular weight of acetaminophen to read 151.17 as per USP 23.

Please revise your labels and labeling, as instructed above, and submit final print container labels and insert labeling.
Firm informed via telephone (see telecon dated 3-5-96)

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's 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.	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			
<i>PROPRIETARY NAME</i>		X	
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
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
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	
Error Prevention Analysis: 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)			x
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.			

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The USP name, Hydrocodone Bitartrate and Acetaminophen Tablets, was confirmed in USP 23.
2. There is no NDA for this drug product. The RLD is Vicodin (Knoll) and the labeling was based on the Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP.
3. The firm will market container sizes of 100s and 1000s for both the 5 mg/500 mg and 7.5 mg/750 mg tablet strengths.
4. Storage/dispensing recommendations:
 RLD: CRT 15⁰-30⁰C (59⁰-86⁰F); tight, light-resistant
 ANDA: same
 USP: Preserve in tight, light-resistant containers
5. As of 12-13-95 the holder of this ANDA is Mallinckrodt Chemical, Inc. King Pharmaceuticals, Inc. will continue to be the manufacturer for this drug product.

6. The 7.5 mg/750 mg tablet is now white thus the agent which was previously listed in the listing of the inactives () is no longer listed.
-
-

Primary Reviewer

Date

Acting Team Leader,
Labeling Review Branch

Date

cc:

ANDA 40-084/S-006

DUP/DIVISION FILE

aev/2/15/96

see x:\new\firmam\king\ltrs&rev\40084S06.NA



**APPEARS THIS WAY
ON ORIGINAL**

D.V.

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

Date of Review: 2-15-96 Date of Submission: 7-25-95

Primary Reviewer: Adolph Vezza

Secondary Reviewer:

ANDA Number: 40-084/S-004 Review Cycle: FIRST

Applicant's Name [as seen on 356(h)]: King Pharmaceuticals, Inc.

Manufacturer's Name (If different than applicant): applicant

Proprietary Name:

Established Name: Hydrocodone Bitartrate and Acetaminophen
Tablets USP, 7.5 mg/750 mg

**LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE
CHEMISTRY COMMENTS TO THE FIRM:**

[NOTE: These deficiencies can be located on the x-drive as
detailed in notes from Ted Sherwood regarding the New X-Drive]

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

1. CONTAINER: 1000s

- a. Place an asterisk after the word "BITARTRATE" in the established name.
- b. Delete the "(Warning:...)" statement after the established name.
- c. Place an asterisk immediately before the "(Warning:...)" statement in the "Each Tablet..." statement. [i.e. *(Warning:...)]

2. INSERT

a. GENERAL COMMENT

Place the asterisk before the parenthesis in the

"Warning..." statement [*(Warning...)] throughout the insert.

b. DESCRIPTION

Revise the molecular weight of acetaminophen to read 151.17 as per USP 23.

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

Please note that the firm has already been made aware of these labeling deficiencies by telephone (see TELECON dated 3-1-96).

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's 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.	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			
<i>PROPRIETARY NAME</i>		X	
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
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
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	
Error Prevention Analysis: 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)			x
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.			

NOTES/QUESTIONS TO THE CHEMIST:

The firm has been made aware of the labeling deficiencies by telephone (see TELECON dated 3-1-96).

FOR THE RECORD:

1. The USP name, Hydrocodone Bitartrate and Acetaminophen Tablets, was confirmed in USP 23.
2. There is no NDA for this drug product. The RLD is Vicodin ES (Knoll) and the labeling was based on the Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP.
3. The firm will market container sizes of 100s (5 mg/500 mg and 7.5 mg/750 mg) and 1000s (7.5 mg/750 mg).
4. Storage/dispensing recommendations:

RLD: CRT 15⁰-30⁰C (59⁰-86⁰F); tight, light-resistant

ANDA: same

USP: Preserve in tight, light-resistant containers

5. As of 12-13-95 the holder of this ANDA is Mallinckrodt Chemical, Inc. King Pharmaceuticals, Inc. will continue to be the manufacturer for this drug product.
 6. The 7.5 mg/750 mg tablet is now white thus the _____ agent which was previously listed in the listing of the inactives (_____ is no longer listed.
 7. The firm was made aware of the labeling deficiencies by telephone (see TELECON dated 3-1-96).
-
-

Primary Reviewer

Date

Acting Team Leader,
Labeling Review Branch

Date

cc:

ANDA 40-084/S-004
DUP/DIVISION FILE
aev/3/4/96

see x:\new\firmSAM\king\ltrs&rev\40084S04.NA



**APPEARS THIS WAY
ON ORIGINAL**

REVIEW OF PROFESSIONAL LABELING #2

AMENDMENTS TO SUPPLEMENTS

FPL

DATE OF REVIEW: June 3, 1996

ANDA #: 40-084/S-006
40-084/S-004

NAME OF FIRM: Mallinckrodt Chemical, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets
USP, 5 mg/500 mg and 7.5 mg/750 mg

DATE OF SUBMISSION: April 30, 1996

COMMENTS: May 29, 1996

Container (1000s): Satisfactory in FPL

Insert: Satisfactory in FPL

RECOMMENDATIONS:

Inform the firm of the above comments.

NOTE TO CHEMIST:

From a labeling standpoint, the supplements may be approved.

FOR THE RECORD:

1. These supplemental applications provide for the labeling associated with a new package size, 1000's.
2. The firm made changes to reflect the transfer of ownership from King Pharmaceuticals to Mallinckrodt which were found to be acceptable.

cc: ANDA 40-084/S-006
40-084/S-004

Dup/Division File
HFD-613/CHoppes/Avezza (no cc:)
HFD-600/RF
njg/6/3/96/x:\...\40084s06.ap
Review

Handwritten notes:
Done for 1/5-3/96
Alloges 6/1/96

D:J

REVIEW OF PROFESSIONAL LABELING # 1

SUPPLEMENT

DRAFT - Container Labels, Carton and Insert Labeling

DATE OF REVIEW: 2-20-96

ANDA #: 40-084/S-008

NAME OF FIRM: King Pharmaceuticals, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets,
USP

DATE OF SUBMISSION: December 8, 1995

COMMENTS:

CONTAINER: 3s (sample), 100s, 1000s

1. Place an asterisk (superscript) after the word "BITARTRATE" in the established name and immediately before the "(Warning...)" statement. [i.e. *(Warning:...)]
2. We note that you have not indicated in your submission that the closure system for the 3s container size is CRC. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use). Your proposed container of 3 appears to be in this category. We believe that this package must comply with the Act. Please comment.

UNIT DOSE BLISTER:

1. Relocate the asterisk in the "Warning:..." statement to appear immediately before the parenthesis. See comment 1. above.
2. "Tablet" rather than "".

See comment 1. under CONTAINER.

INSERT:

1. TITLE

Place an asterisk (superscript) after the word "BITARTRATE" in the established name.

2. DESCRIPTION

- a. Place an asterisk in the "Warning:... " statement immediately before the parenthesis.
- b. Revise the molecular weight of acetaminophen to read 151.17 as per USP 23.

3. HOW SUPPLIED

Revise to read:

...capsule shaped tablet, scored...

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their labels and labeling, then prepare and submit final print labels and labeling. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

NOTE TO CHEMIST:

Please see comment 2 under CONTAINER.

FOR THE RECORD:

1. There is no NDA for this drug product. The RLD is Lorcet 10/650 (Mikart) and the labeling was based on the Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP (revised 4/94).
2. There are no outstanding patents or exclusivities for this drug product.
3. Storage/dispensing recommendations:
RLD: CRT 15⁰-30⁰C (59⁰-86⁰F); tight, light-resistant
ANDA: same
USP: Preserve in tight, light-resistant containers
4. As of 12-13-95 the holder of this ANDA is Mallinckrodt Chemical, Inc. King Pharmaceuticals, Inc. will continue to be the manufacturer for this drug product.

5. The description of the tablet as listed in the HOW SUPPLIED section is accurate (page 245 Vol. 5.1).
6. The listing of 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 appearing on page 105 (Volume 5.1).
7. This product will be marketed in container sizes 3s (sample), 100s, 1000s and

Adolph Vezza

cc: ANDA 40-084/S-008
Dup/Division File
HFD-613/AVezza/JGrace (no cc:)
HFD-600/RF
aev/2/20/96 x:\new\firmam\king\ltrs&rev\50084S08.NA
Review

**APPEARS THIS WAY
ON ORIGINAL**

DIV

REVIEW OF PROFESSIONAL LABELING # 2

SUPPLEMENTAL AMENDMENT

DRAFT - Container Labels and Insert Labeling

DATE OF REVIEW: 8-12-96

ANDA #: 40-084/S-008

NAME OF FIRM: Mallinckrodt Chemical, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets,
USP 10 mg/650 mg

DATE OF SUBMISSION: August 1, 1996

COMMENTS:

CONTAINER: 3s (sample), 100s, 1000s

Satisfactory

INSERT:

DOSAGE AND ADMINISTRATION

Revise the last two sentences as follows:

The usual adult dosage is one tablet every four hours as needed for pain. The total 24 hour dose should not exceed 6 tablets.

NOTE TO CHEMIST:

If chemistry is satisfactory, please let the labeling reviewer know to relay the above deficiency by telephone rather than including it with a chemistry deficiency letter.

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their package insert labeling, then prepare and submit final print. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

FOR THE RECORD:

1. There is no NDA for this drug product. The RLD is Lorcet 10/650 (Mikart) and the labeling was based on the Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP (revised 4/94).
2. There are no outstanding patents or exclusivities for this drug product.
3. Storage/dispensing recommendations:
RLD: CRT 15⁰-30⁰C (59⁰-86⁰F); tight, light-resistant
ANDA: same
USP: Preserve in tight, light-resistant containers
4. As of 12-13-95 the holder of this ANDA is Mallinckrodt Chemical, Inc. King Pharmaceuticals, Inc. will continue to be the manufacturer for this drug product.
5. The description of the tablet as listed in the HOW SUPPLIED section is accurate (page 245 Vol. 5.1).
6. The listing of 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 appearing on page 105 (Volume 5.1).
7. The firm had planned to market this product will be marketed in container sizes 3s (sample), 100s, 1000s and _____ The firm requested that the _____ container/closure system be eliminated from consideration in this amendment. Reference to the _____ package has been deleted from HOW SUPPLIED.
8. The firm has committed to marketing the 3s size with a child-resistant closure.

Charlie Hoppes

cc: ANDA 40-084/S-008
Dup/Division File
HFD-613/CHoppes/AVezza (no cc:)
HFD-600/RF
njg/8/12/96/x:\...\40084s08.na2
Review

DN

REVIEW OF PROFESSIONAL LABELING # 3

SUPPLEMENTAL AMENDMENT

FPL - Insert Labeling

DATE OF REVIEW: 9-17-96

ANDA #: 40-084/S-008

NAME OF FIRM: Mallinckrodt Chemical, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets
USP, 10 mg/650 mg

DATE OF SUBMISSION: September 11, 1996

COMMENTS:

CONTAINER: 3s (sample), 100s, 1000s

Satisfactory (8/1/96 submission)

INSERT:

Satisfactory (This submission)

RECOMMENDATIONS:

From a labeling standpoint, the supplement may be approved.

FOR THE RECORD:

1. There is no NDA for this drug product. The RLD is Lorcet 10/650 (Mikart) and the labeling was based on the Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP (revised 4/94).
2. There are no outstanding patents or exclusivities for this drug product.
3. Storage/dispensing recommendations:
RLD: CRT 15⁰-30⁰C (59⁰-86⁰F); tight, light-resistant
ANDA: same
USP: Preserve in tight, light-resistant containers
4. As of 12-13-95 the holder of this ANDA is Mallinckrodt Chemical, Inc. King Pharmaceuticals, Inc. will continue to be the manufacturer for this drug product.

5. The description of the tablet as listed in the HOW SUPPLIED section is accurate (page 245 Vol. 5.1).
6. The listing of 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 appearing on page 105 (Volume 5.1).
7. The firm had planned to market this product in container sizes 3s (sample), 100s, 1000s and _____
_____ The firm requested that the _____ container/closure system be eliminated from consideration in this amendment. Reference to the _____ package has been deleted from HOW SUPPLIED.
8. The firm has committed to marketing the 3s size with a child-resistant closure.
9. The labeling comment that was the subject of the second review for this supplement was detailed to the firm by telephone on 8/26/96. The firm submitted FPL with the correction in this submission.

Charlie Hoppes

cc: ANDA 40-084/S-008
Dup/Division File
HFD-613/CHOPPES/LGOLSON/JGRACE (no cc:)
HFD-600/RF
njg/9/17/96/x:\...\40084s08.na2
Review

**APPEARS THIS WAY
ON ORIGINAL**

D.J

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

Date of Review: 2-12-96 Date of Submission: 6-30-95

Primary Reviewer: Adolph Vezza

Secondary Reviewer:

ANDA Number: 40-084/S-002 Review Cycle: FIRST

Applicant's Name [as seen on 356(h)]: King Pharmaceuticals, Inc.

Manufacturer's Name (If different than applicant): applicant

Proprietary Name: Anexsia® 10/660

Established Name: Hydrocodone Bitartrate and Acetaminophen
Tablets USP

**LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE
CHEMISTRY COMMENTS TO THE FIRM:**

[NOTE: These deficiencies can be located on the x-drive as
detailed in notes from Ted Sherwood regarding the New X-Drive]

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

1. CONTAINER: 100s and 1000s

a. Delete the asterisk after the word "Bitartrate" in
the "Each Tablet Contains:" statement and relocate
it to after the word "BITARTRATE" in the
established name.

b. Relocate the asterisk from before the word
"WARNING" and relocate it to before the
parenthesis - not as a superscript (i.e.
*(WARNING:...)).

2. INSERT

a. GENERAL COMMENT

The requirements of 21 CFR 201.10(g)(1) must be

met. The established name is to appear at least once in each column in association with the proprietary name.

b. DESCRIPTION

- i. Place an asterisk immediately before the statement "(Warning...)" [see 1.b.].
- ii. Revise the molecular weight of acetaminophen to read 151.17 as per USP 23.

c. OVERDOSAGE

Treatment - Fourth paragraph, first sentence.

...opioid overdose. (spelling)

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's 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.	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			
<i>PROPRIETARY NAME</i>	X		
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	
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			

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	
Error Prevention Analysis: 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.			

NOTES/QUESTIONS TO THE CHEMIST:

1. I was unable to confirm the description of the debossing of the tablet as presented in the HOW SUPPLIED section anywhere else in the submission. Please verify its accuracy or request the firm to correct the omission.
2. In doing my review I noticed that a bio waiver had been granted 12-5-95. Please modify your chem review with this in mind.

FOR THE RECORD:

1. []

2. The USP name, Hydrocodone Bitartrate and Acetaminophen Tablets, was confirmed in USP 23.
 3. There is no NDA for this drug product. The RLD is Vicodin ES (Knoll) and the labeling was based on the Labeling Guidance for Hydrocodone Bitartrate and Acetaminophen Tablets USP.
 4. A petition has been granted to market this strength (10 mg/660 mg) tablet.
 5. There are no active patents or exclusivities for this drug product.
 6. A bio waiver was granted on 12-5-95.
 7. The tablet is scored (p. 245 V. 4.2) as is the reference listed drug.
 8. The listing of inactive ingredients as listed in the insert has been confirmed (p. 166 V. 4.1).
 9. The firm will market container sizes of 100s and 1000s.
 10. I was unable to confirm the description of the tablet's debossing as described in the HOW SUPPLIED section. I noted this in NOTES TO THE CHEMIST.
 11. As of 12-13-95 the holder of this ANDA is Mallinckrodt Chemical, Inc. King Pharmaceuticals, Inc. will continue to be the manufacturer for this drug product.
 12. Storage/dispensing recommendations:
RLD: CRT 15⁰-30⁰C (59⁰-86⁰F); tight, light-resistant
ANDA: same
USP: Preserve in tight, light-resistant containers
-
-

Primary Reviewer

Date

Acting Team Leader,
Labeling Review Branch

Date

cc:

ANDA 40-084/S-002
DUP/DIVISION FILE
aev/2/12/96

see x:\new\firm\king\ltrs&rev\40084S02.NA



DIU

REVIEW OF PROFESSIONAL LABELING

AMENDMENTS TO SUPPLEMENT (Minor)

FPL

DATE OF REVIEW: June 20, 1996

ANDA #: 40-084/S-002

NAME OF FIRM: Mallinckrodt Chemical, Inc.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets
USP, 10 mg/660 mg.

PROPRIETARY NAME: ANEXIA

DATE OF SUBMISSION: May 31, 1996 (minor amendment)
original: June 30, 1995
last amendment: November 27, 1995

COMMENTS:

Container (100s and 1000s): Satisfactory in FPL

Insert: Satisfactory in FPL

RECOMMENDATIONS:

Approve the supplement.

FOR THE RECORD:

1. These supplemental applications provide for the labeling associated with a new an additional new product strength of 10 mg/660 mg.
2. The firm made changes to reflect the transfer of ownership from King Pharmaceuticals to Mallinckrodt which were found to be acceptable.

cc: ANDA 40-084/S-002
Dup/Division File
HFD-613/JGrace/AVezza (no cc:)
HFD-600/RF
6/20/96/x:\new\firmssam\mallink\letrs&rev\40084s02.ap
Review

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-084/S-001; S-002; S-003; S-004;
S-005; S-006; S-007; S-008; S-009;
S-010; S-011; S-012; S-013; S-014;
S-015; S-016; S-017; S-018; S-019;
S-020; S-021; S-022; S-023; S-024;
S-028**

CHEMISTRY REVIEW(S)

02

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

SUPPLEMENT REVIEW

ANDA 40-084/S-001, S-002

NAME AND ADDRESS OF APPLICANT:

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, TN 37620

PURPOSE OF SUPPLEMENT:

- S-001: New tablet strength containing 10 mg. Hydrocodone Bitartrate and 660 mg. Acetaminophen.
- S-002: Labeling Revision

DATE(S) OF SUBMISSION(S)

Firm:

6.30.95: Original submission

Note: It was found during the review of this supplement that the submission was incomplete. Certain documentation could not be found in the blue jackets. The CSO requested the applicant to send the remainder of the supplement on 11.27.95. The necessary copy was received and filed on 11.28.95.

PHARMACOLOGICAL CATEGORY :Analgesic

TRADE NAME Anexsia®10/660

NONPROPRIETARY NAME Hydrocodone Bitartrate and Acetaminophen Tablets, USP

DOSAGE FORM Tablets

POTENCY 10 mg Hydrocodone Bitartrate and 660 mg Acetaminophen

R_x OR OTC: R_x

<u>SAMPLES</u>	<u>RELATED IND/NDA/DMF</u>	<u>STERILIZATION</u>
N/A	ANDA 89-160 & 89-725 DMF — & DMF —	N/A

LABELING Labeling review - Not satisfactory, A Vezza, 2.12.96

Redacted 8

Page(s) of trade

secret and /or

confidential

commercial

information

012

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

SUPPLEMENT REVIEW

ANDA 40-084/S-001, S-002

NAME AND ADDRESS OF APPLICANT:

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, TN 37620

PURPOSE OF SUPPLEMENT:

- S-001: New tablet strength containing 10 mg. Hydrocodone Bitartrate and 660 mg. Acetaminophen.
- S-002: Labeling Revision

DATE(S) OF SUBMISSION(S)

Firm:

- 06.03.95: Original submission
- 05.31.96: Amendment **Subject of this review**

FDA:

- 04.18.96: NA letter#1

PHARMACOLOGICAL CATEGORY :Analgesic

TRADE NAME None

NONPROPRIETARY NAME Hydrocodone Bitartrate and Acetaminophen Tablets, USP

DOSAGE FORM Tablets

POTENCY 10 mg Hydrocodone Bitartrate and 650 mg Acetaminophen

R_x OR OTC: R_x

<u>SAMPLES</u>	<u>RELATED IND/NDA/DMF</u>	<u>STERILIZATION</u>
N/A	ANDA 89-160 & 89-725 DMF _____ & DMF _____	N/A

LABELING Labeling review - Satisfactory, A Vezza, 6.20.96

BIOEQUIVALENCY STATUS Waiver requested, page 65; Acceptable - J. Henderson, 12.13.95. (Note the product is rated AA.)

Redacted 3

Page(s) of trade

secret and /or

confidential

commercial

information

9, N

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

SUPPLEMENT REVIEW

ANDA 40-084/S-007, S-008

NAME AND ADDRESS OF APPLICANT:

Mallinckrodt Chemical, Inc.
Attention: Charles H. Smith
Chesterfield, MO 63017-1777

PURPOSE OF SUPPLEMENT:

- S-007: New tablet strength containing 10 mg. Hydrocodone Bitartrate and 650 mg. Acetaminophen.
- S-008: Labeling Revision incorporating additional product strength.

DATE(S) OF SUBMISSION(S)

Firm:

- 12.8.95: Original submission
- 8.01.96: Amendment **Subject of this review**
- 8.19.96: Amendment **Subject of this review**
- 8.23.96: Amendment **Subject of this review**

FDA:

- 6.10.96: NA letter

PHARMACOLOGICAL CATEGORY :Analgesic

TRADE NAME None

NONPROPRIETARY NAME Hydrocodone Bitartrate and Acetaminophen Tablets, USP

DOSAGE FORM Tablets

POTENCY 10 mg Hydrocodone Bitartrate and 650 mg Acetaminophen

R_x OR OTC: R_x

<u>SAMPLES</u>	<u>RELATED IND/NDA/DMF</u>	<u>STERILIZATION</u>
N/A	ANDA 89-160 & 89-725 DMF — & DMF —	N/A

LABELING Labeling review - Not satisfactory; C. Hoppes - 8.12.96
FPL satisfactory 9.17.96 CHoppes

Redacted

5

Page(s) of trade

secret and /or

confidential

commercial

information

dw

**OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II**

SUPPLEMENT REVIEW

ANDA 40-084/S-007, S-008

NAME AND ADDRESS OF APPLICANT:

Mallinckrodt Chemical, Inc.
Attention: Charles H. Smith
Chesterfield, MO 63017-1777

PURPOSE OF SUPPLEMENT:

S-007: New tablet strength containing 10 mg. Hydrocodone Bitartrate and 650 mg. Acetaminophen.

S-008: Labeling Revision incorporating additional product strength.

DATE(S) OF SUBMISSION(S)

Firm:

12.8.95: Original submission **Subject of this review**

PHARMACOLOGICAL CATEGORY :Analgesic

TRADE NAME None

NONPROPRIETARY NAME Hydrocodone Bitartrate and Acetaminophen Tablets, USP

DOSAGE FORM Tablets

POTENCY 10 mg Hydrocodone Bitartrate and 650 mg Acetaminophen

R_x OR OTC: R_x

<u>SAMPLES</u>	<u>RELATED IND/NDA/DMF</u>	<u>STERILIZATION</u>
----------------	----------------------------	----------------------

N/A	ANDA 89-160 & 89-725 DMF _____ & DMF _____	N/A
-----	---	-----

LABELING Labeling review - Not satisfactory Vezza, 2.20.96

BIOEQUIVALENCY STATUS Waiver requested, page 65; Acceptable - J. Henderson, 5.3.96. (Note the product is rated AA.)

ESTABLISHMENT INSPECTION Facility found acceptable during pre-approval inspection. EER requested for outside facilities.

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

Redacted 11

Page(s) of trade

secret and /or

confidential

commercial

information

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

SUPPLEMENT REVIEW

ANDA 40-084/S-003

NAME AND ADDRESS OF APPLICANT:

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, TN 37620

New holder of ANDA

Mallinckrodt Chemical, Inc.
Attention: Charles H. Smith
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

PURPOSE OF SUPPLEMENT:

S-003: New packaging configuration - 1000 count bottles of 7.5 mg/750 mg strength product.

DATE(S) OF SUBMISSION(S)

Firm:

7.25.95: Original submission **Subject of this review**

Note: The ANDA has been transferred to Mallinckrodt Chemical, Inc.

PHARMACOLOGICAL CATEGORY :Analgesic

TRADE NAME Anexsia®10/660

NONPROPRIETARY NAME Hydrocodone Bitartrate and Acetaminophen Tablets, USP

DOSAGE FORM Tablets

POTENCY 7.5 mg Hydrocodone Bitartrate and 750 mg Acetaminophen

R_x OR OTC: R_x

SAMPLES

RELATED IND/NDA/DMF

STERILIZATION

N/A

ANDA 89-160 & 89-725
DMFs

N/A

Redacted 3

Page(s) of trade

secret and /or

confidential

commercial

information

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

SUPPLEMENT REVIEW

ANDA 40-084/S-005

NAME AND ADDRESS OF APPLICANT:

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, TN 37620

New holder of ANDA

Mallinckrodt Chemical, Inc.
Attention: Charles H. Smith
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

PURPOSE OF SUPPLEMENT:

S-005: New packaging configuration - 1000 count bottles of 5 mg/500 mg strength product.

DATE(S) OF SUBMISSION(S)

Firm:

9.1.95: Original submission **Subject of this review**

Note: The ANDA has been transferred to Mallinckrodt Chemical, Inc.

PHARMACOLOGICAL CATEGORY :Analgesic

TRADE NAME None

NONPROPRIETARY NAME Hydrocodone Bitartrate and Acetaminophen Tablets, USP

DOSAGE FORM Tablets

POTENCY 5 mg Hydrocodone Bitartrate and 500 mg Acetaminophen

R_x OR OTC: R_x

SAMPLES

RELATED IND/NDA/DMF

STERILIZATION

N/A

ANDA 89-160 & 89-725
DMFs

N/A

Redacted 4

Page(s) of trade

secret and /or

confidential

commercial

information

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

SUPPLEMENT REVIEW

ANDA 40-084/S-003, S-005

NAME AND ADDRESS OF APPLICANT:

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, TN 37620

New holder of ANDA

Mallinckrodt Chemical, Inc.
Attention: Charles H. Smith
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

PURPOSE OF SUPPLEMENT:

S-003: New packaging configuration - 1000 count bottles of 7.5 mg/750 mg strength product.

S-005: New packaging configuration - 1000 count bottles of 5 mg/500 mg strength product.

DATE(S) OF SUBMISSION(S)

Firm:

For S-003

7.25.95: Original submission
4.30.96: Labeling amendment

For S-005

9.1.95: Original submission
4.30.96: Labeling amendment

Note: The ANDA has been transferred to Mallinckrodt Chemical, Inc.

PHARMACOLOGICAL CATEGORY :Analgesic

TRADE NAME Anexsia®10/660

NONPROPRIETARY NAME Hydrocodone Bitartrate and Acetaminophen Tablets, USP

DOSAGE FORM Tablets

POTENCY: 7.5 mg Hydrocodone Bitartrate and 750 mg Acetaminophen and 5 mg /500 mg

R_x OR OTC: R_x

<u>SAMPLES</u>	<u>RELATED IND/NDA/DMF</u>	<u>STERILIZATION</u>
N/A	ANDA 89-160 & 89-725 DMFs	N/A

LABELING Profession labeling review not satisfactory, A Vezza, 2.15.96; satisfactory, A. Vezza, 6.3.96

BIOEQUIVALENCY STATUS N/A

ESTABLISHMENT INSPECTION N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

Please see previous review (#1) for review of CMC changes, dated 1.31.96.

The labeling review is satisfactory, A. Vezza, 6.3.96.

STABILITY page 37; Satisfactory per review #1, dated 1.31.96

REMARKS AND CONCLUSION :The supplemental application is satisfactory in CMC and labeling and it may be approved.

RECALLS None

ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt Yes _____ No x

If no, explain reason(s) below: Application submission was telephone amended (labeling) and was given minor status.

<u>Reviewer</u>	<u>Date Completed</u>
U. V. Venkataram, Ph.D.	6.7.96

cc: ANDA #40084
Division File
Field Copy

Endorsements:

HFD-647/UVVenkataram/6.7.96 U.V. Venkataram 6/29/96
HFD-647/JSimmons/6.25.96
x:\wpfile\branch7\venkatar\final\40084s03.rlu
F/T by pah/6.28.96
a:\40084s03.rf
X:\new\firmam\mallinc\ltrs&rev\

Redacted 2

Page(s) of trade

secret and /or

confidential

commercial

information

OFFICE OF GENERIC DRUGS
REVIEW OF SUPPLEMENT TO
ABBREVIATED NEW DRUG APPLICATION

1. ANDA NUMBER

40-084/S-010, S-011, S-012, S-013, S-014, S-015

2. NAME AND ADDRESS OF APPLICANT

Mallinckrodt Inc.,
Attention: Connie McNabb
675 McDonnell Boulevard
P. O. Box 5840
St. Louis MO-63134

3. PURPOSE OF AMENDMENT/SUPPLEMENT

Changes in:

S-010:

[

]

S-011: Formulation revision-change in components and composition.

S-012: Manufacturing revision-change from _____ to _____ and changes in manufacturing processes and procedures.

S-013: Controls revision-change in in-process specifications for major formulation and process changes.

S-014: Package revision for change in the container/closure system including HDPE bottles of 100 count, HDPE bottles of 500 count and unit dose blister packaging.

4. DATE(S) OF SUBMISSION(S)

Firm:

6/30/1998 Supplements, Original
9/29/1998 Amendments, (unsolicited)

12. STERILIZATION

N/A

13. LABELING

Acceptable per review by A. Vezza dated 6/10/99.

14. BIOEQUIVALENCY STATUS

Review Status: Satisfactory

Reviewed by Carol Kim, Bio-Reviewer and the letter sent on 10/29/1998.

The firm has submitted dissolution data for its drug product, Hydrocodone Bitartrate and Acetaminophen Tablets, USP, (7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg), applying the following conditions:

Conditions for Dissolution Testing

Method of dissolution	USP 23, Apparatus II (paddle)
Time/ Speed	30 minutes/ 50 rpm
No. of Units Tested	12
Medium	Phosphate Buffer, pH 5.8
Temperature	37°C
Volume	900 ml
Specifications	NLT 80% (Q) is dissolved in 30 minutes
Assay Methodology	
Reference Product	King Pharmaceuticals, Inc.'s Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg

15. ESTABLISHMENT INSPECTION

Review Status: Not Satisfactory

EER-Report Attached

CGMP certificates submitted on pages 433 & 434

Acceptable for all 4

Facilities:

Mallinkrodt Inc
58, Pearl Street
P.O.Box P
Hobart, NY 13788

Mallinkrodt Inc

13 Railroad Ave
Hobart, NY 13788

There are three more facilities used for packaging and labeling, distribution and chemical testing. For all these facilities EER report is acceptable.

Hobart, NY 13788

The facility for the packaging and Labeling of drug product at:

Mallinckrodt, Inc.
P.O.Box G
18 Cornell Avenue
Hobart, NY 13788

The facility for the holding distribution of drug product at:

Mallinckrodt, Inc.
3600 North Second Street
St. Louis, MO 63147

Contract facilities:



Comments:

1. We note that there are two facilities for the manufacturing, processing, packaging and labeling, testing, stability, and release of drug product on page 431. Please provide in detail the functions for each of the manufacturing sites (58 Pearl Street and 13 Railroad Avenue).
2. We note that the manufacturing site for _____ is located at _____ in page 221. However, the manufacturing and control site for drug substance was listed as _____ in the same page. Please clarify.

16. COMPONENTS, COMPOSITION, MANUFACTURING & CONTROLS:

Not Satisfactory

Redacted _____

Page(s) of trade

secret and /or

confidential

commercial

information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs

Abbreviated New Drug Supplemental Application Review

ANDA Global (See Attachment)

CHEMIST REVIEW no. 1

NAME AND ADDRESS OF APPLICANT:

Mallinckrodt Inc.
Attention: Melissa Cay
675 McDonnell Blvd
St Louis, Missouri 63134

PURPOSE OF AMENDMENT/SUPPLEMENT

CBE-30 provides for the addition of _____ as

DATE(S) OF SUBMISSION(S)

30-NOV-2001: Original Submission

PHARMACOLOGICAL CATEGORY

See Attachment

TRADE NAME

N/A

NONPROPRIETARY NAME

See Attachment

DOSAGE FORM

See Attachment

POTENCY

See Attachment

R_x OR OTC

Rx

SAMPLES

N/A

RELATED IND/NDA/DMF

N/A

STERILIZATION

N/A

LABELING - N/A

BIOEQUIVALENCY STATUS - N/A

ESTABLISHMENT INSPECTION

07-JAN-2002: Acceptable

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

The firm proposes no changes to the CCMCs.

PACKAGING

The firm proposes _____ as _____

(page 08):

The ~~_____~~GMP certification appears on page 09. The firm specifies that the last FDA compliance inspection was 14-OCT-1999 through 30-NOV-1999.

Mallinckrodt specifies in the cover letter that the same currently approved ~~_____~~ will be used by ~~_____~~ DMF cross references are attached on page 07.

STABILITY - No Proposed Changes

The firm certifies on page 012 to place the first production lot of the ~~_____~~ on long-term stability according to the currently approved stability protocol. Yearly after that, one production lot will be added to the program, if one is manufactured, and results will be submitted in the annual reports.

The firm retains the currently approved 24 months expiration period for the ~~_____~~

REMARKS AND CONCLUSION

The firm's application meets the SUPAC Stand Alone Packaging Change requirements.

Recommend Approval

RECALLS

N/A

Reviewer

D. Roselle, Ph.D.

Date Completed

28-FEB-2002

ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt? Yes

**APPEARS THIS WAY
ON ORIGINAL**

Globals Attachment:

40-084/S-016: Hydrocodone Bitartrate/Acetaminophen
40-201/S-007: Hydrocodone Bitartrate/Acetaminophen
40-400/S-001: Hydrocodone Bitartrate/Acetaminophen
40-419/S-001: Acetaminophen/Codeine Phosphate
89-160/S-032: Acetaminophen/Hydrocodone Bitartrate
89-725/S-027: Acetaminophen/Hydrocodone Bitartrate

**APPEARS THIS WAY
ON ORIGINAL**

ANDA 40-084/S-017, S-018

NAME AND ADDRESS OF APPLICANT:

Mallinckrodt Inc.
Attention: Melissa Cay
675 McDonnell Blvd.
P.O. 5840
St. Louis, MO 63134-0840

PURPOSE OF AMENDMENT/SUPPLEMENT

S-017 Provide for the addition of 30, 60, 90 and 120 count
bottle sizes

S-018 Label Revision

DATE(S) OF SUBMISSION(S)

January 11, 2002

PHARMACOLOGICAL CATEGORY

Narcotic Analgesic

TRADE NAME

ANEXIA

NONPROPRIETARY NAME

Hydrocodone Bitartrate and Acetaminophen

DOSAGE FORM

Tablet

RX OR OTC

Rx

POTENCY

7.5 mg/750 mg; 10 mg/650 mg; 10 mg/660 mg

SAMPLES

N/A

RELATED IND/NDA/DMF

See under packaging

STERILIZATION

N/A

LABELING

Deficient on 1/23/02 by Chan Park

BIOEQUIVALENCY STATUS

N/A

ESTABLISHMENT INSPECTION

N/A

**APPEARS THIS WAY
ON ORIGINAL**

Redacted 5

Page(s) of trade

secret and /or

confidential

commercial

information

ANDA 40-084/S-017, S-018

NAME AND ADDRESS OF APPLICANT:

Mallinckrodt Inc.
Attention: Melissa Cay
675 McDonnell Blvd.
P.O. 5840
St. Louis, MO 63134-0840

PURPOSE OF AMENDMENT/SUPPLEMENT

S-017 Provide for the addition of 30, 60, 90 and 120 count
bottle sizes

S-018 Label Revision

DATE(S) OF SUBMISSION(S)

January 11, 2002
July 1, 2002
July 24, 2002
August 26, 2002

PHARMACOLOGICAL CATEGORY

Narcotic Analgesic

TRADE NAME

ANEXIA

NONPROPRIETARY NAME

Hydrocodone Bitartrate and Acetaminophen

DOSAGE FORM

Tablet

RX OR OTC

Rx

POTENCY

7.5 mg/750 mg; 10 mg/650 mg; 10 mg/660 mg

SAMPLES

N/A

RELATED IND/NDA/DMF

See under packaging

STERILIZATION

N/A

LABELING

Acceptable on 10/1/02 by Chan Park

BIOEQUIVALENCY STATUS

N/A

ESTABLISHMENT INSPECTION

N/A

APPEARS THIS WAY
ON ORIGINAL

Redacted

5

Page(s) of trade

secret and /or

confidential

commercial

information

ANDA 40-084/S-019

NAME AND ADDRESS OF APPLICANT:

Mallinckrodt Inc.
Attention: Marianne Rob
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134-0840

PURPOSE OF AMENDMENT/SUPPLEMENT

S-019 Provides for _____

DATE(S) OF SUBMISSION(S)

April 9, 2002 Original

PHARMACOLOGICAL CATEGORY

Narcotic Analgesic

TRADE NAME

N/A

NONPROPRIETARY NAME

Hydrocodone Bitartrate and Acetaminophen

DOSAGE FORM

Tablet

RX OR OTC

Rx

POTENCY

7.5 mg/750 mg; 10 mg/650 mg; 10 mg/660 mg

SAMPLES

N/A

RELATED IND/NDA/DMF

N/A

STERILIZATION

N/A

LABELING

N/A

BIOEQUIVALENCY STATUS

N/A

ESTABLISHMENT INSPECTION

N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

[]

Redacted

3

Page(s) of trade

secret and /or

confidential

commercial

information

ANDA 40-084/S-021

NAME AND ADDRESS OF APPLICANT:

Mallinckrodt Inc.
Attention: Marianne Rob
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134-0840

PURPOSE OF AMENDMENT/SUPPLEMENT

S-021 Provides for _____
_____ as an in-process specification.

DATE(S) OF SUBMISSION(S)

November 20, 2002 Original

Signed

PHARMACOLOGICAL CATEGORY

Narcotic Analgesic

TRADE NAME

N/A

NONPROPRIETARY NAME

Hydrocodone Bitartrate and Acetaminophen

DOSAGE FORM

Tablet

RX OR OTC

Rx

POTENCY

7.5 mg/750 mg; 10 mg/650 mg; 10 mg/660 mg

SAMPLES

N/A

RELATED IND/NDA/DMF

N/A

STERILIZATION

N/A

LABELING

N/A

BIOEQUIVALENCY STATUS

N/A

ESTABLISHMENT INSPECTION

N/A

**APPEARS THIS WAY
ON ORIGINAL**

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

[]

PACKAGING

NA

STABILITY

N/A

REMARKS AND CONCLUSION

Approvable.

RECALLS

Reviewer

A. Langowski

ORDER OF REVIEW:

The application submission(s) covered by this review was taken
in the date order of receipt Yes x

No

If no, explain reason(s) below.

**APPEARS THIS WAY
ON ORIGINAL**

ANDA

See Attached.

NAME AND ADDRESS OF APPLICANT:

Mallinckrodt Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

PURPOSE OF AMENDMENT/SUPPLEMENT

The purpose of the supplements is to ~~_____~~
_____ as an approved in-process control.

DATE(S) OF SUBMISSION(S)

October 27, 2003 - Original Submission

PHARMACOLOGICAL CATEGORY

N/A

TRADE NAME

N/A

NONPROPRIETARY NAME

N/A

DOSAGE FORM

Tablets for
oral administration

POTENCY

N/A

RX OR OTC

Rx

SAMPLES

N/A

RELATED IND/NDA/DMF

N/A

STERILIZATION

N/A

LABELING

No change

BIOEQUIVALENCY STATUS

N/A

ESTABLISHMENT INSPECTION

N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS



PACKAGING

N/A

STABILITY

N/A

REMARKS AND CONCLUSION

[]

RECALLS

N/A

Reviewer

Glen Jon Smith

Team Leader, Team 9

ORDER OF REVIEW:

The application submission(s) covered by this review was taken
in the date order of receipt Yes ___ No X

If no, explain reason(s) below.

Administrative review by Team Leader, since the change is
procedural with no scientific issues to be reviewed.

**APPEARS THIS WAY
ON ORIGINAL**

Attachment:

<u>ANDA No.</u>	<u>Drug Product Name</u>
40-201/S-014	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/500 mg and 10 mg/500 mg
89-725/S-035	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/650 mg
75-983/S-006	Tramadol Hydrochloride Tablets, 50 mg
74-184/S-005	Methadone Hydrochloride Tablets USP, 40 mg
40-084/S-023	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg
89-160/S-039	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg
40-436/S-001	Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg
40-419/S-007	Acetaminophen and Codeine Phosphate Tablets USP, 300 mg/15 mg, 300 mg/30 mg, and 300 mg/60 mg
40-352/S-002	Meperidine Hydrochloride Tablets USP, 50 mg and 100 mg
40-300/S-002	Methylphenidate Hydrochloride Tablets USP, 5 mg, 10 mg, and 20 mg
75-738/S-009	Propoxyphene Napsylate and Acetaminophen Tablets USP, 100 mg/650 mg
75-629/S-003	Methylphenidate Hydrochloride Extended-Release Tablets USP, 10 mg and 20 mg
40-050/S-007	Methadone Hydrochloride Tablets USP, 5 mg and 10 mg
40-405/S-009	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/325 mg
40-409/S-007	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/325 mg
40-400/S-007	Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/325 mg

APPEARS THIS WAY
ON ORIGINAL

ANDA 40-084/S-025

NAME AND ADDRESS OF APPLICANT:

Mallinckrodt Inc.
Attention: Ronald Groman
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134-0840

PURPOSE OF AMENDMENT/SUPPLEMENT

S-025 Provides for a new bulk packaging container/closure configuration.

DATE(S) OF SUBMISSION(S)

June 9, 2004
July 30, 2004-Amendment

PHARMACOLOGICAL CATEGORY

Narcotic Analgesic

TRADE NAME

N/A

NONPROPRIETARY NAME

Hydrocodone Bitartrate and Acetaminophen

DOSAGE FORM

Tablet

RX OR OTC

Rx

POTENCY

7.5 mg/750 mg

SAMPLES

N/A

RELATED IND/NDA/DMF

N/A

STERILIZATION

N/A

LABELING

S-026 - Acceptable 09/29/04

BIOEQUIVALENCY STATUS

N/A

ESTABLISHMENT INSPECTION

N/A

**APPEARS THIS WAY
ON ORIGINAL**

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

The new proposed bulk container is a 2 gallon white HDPE bucket with lid using the same double — bag liner.

PACKAGING

The acceptance specifications for the new configuration are provided. The ~~closure is a screw top with a resealing lid~~; The ~~lid~~ is ~~resealing~~ and the ~~lid~~ is ~~resealing~~. The closure is a screw -top with a resealing lid. The seal is moisture resistant and the lid is classified as CRC.

STABILITY

The firm provided 3 months accelerated and 3 months room temperature data on the proposed bulk container. The data were within the stated specifications. The ~~closure~~ meets the applicable 21 CFR Food Additive Regulations.

The firm submitted an acceptable stability commitment. 7/30/04
The firm has provided a commitment to place one production batch per year on stability at controlled room temperature.

REMARKS AND CONCLUSION

Approvable.

RECALLS

Reviewer
A. Langowski

ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt Yes x
No

If no, explain reason(s) below.

**APPEARS THIS WAY
ON ORIGINAL**

ANDA: See attached

NAME AND ADDRESS OF APPLICANT:

Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Blvd.
P.O. 5840
St. Louis, MO 63134-0840

PURPOSE OF AMENDMENT/SUPPLEMENT

Provides for _____

DATE(S) OF SUBMISSION

December 16, 2003

PHARMACOLOGICAL CATEGORY

Narcotic Analgesic

TRADE NAME

N/A

NONPROPRIETARY NAME

N/A

DOSAGE FORM

Tablet

RX OR OTC

Rx

POTENCY

See attached

SAMPLES

N/A

RELATED IND/NDA/DMF

N/A

STERILIZATION

N/A

LABELING

N/A

BIOEQUIVALENCY STATUS

N/A

ESTABLISHMENT INSPECTION

N/A

**APPEARS THIS WAY
ON ORIGINAL**

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

The firm proposes to eliminate in-process control testing for ~~based on~~ based on historical data. No data were submitted to support the proposed change. It appears they ~~perform the~~ a few tablets and perform the ~~same tests~~. If the results pass, they continue with ~~the same tests~~ and perform the same tests again (at initiation of ~~double testing~~ double testing in effect. The intent of these supplements is to eliminate the ~~only based on historical data~~ only based on historical data. In light of this, we could recommend approval. The firm will submit the revised batch record test sheet in the next annual report.

PACKAGING

N/A

STABILITY

N/A

REMARKS AND CONCLUSION

Approvable.

RECALLS

Reviewer

A. Langowski

ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt Yes x
No

If no, explain reason(s) below.

APPEARS THIS WAY
ON ORIGINAL

Attachment:

<u>ANDA No.</u>	<u>Drug Product Name</u>
40-050/S-007	Methadose Oral Tablets (Methadone Hydrochloride Tablets USP, 5 mg and 10 mg)
40-084/S-024	Hydrocodone Bitartrate and Acetaminophen Tablets USP, (7.5 mg/750 mg, 10 mg/650 mg and 10 mg/660 mg)
40-201/S-015	Hydrocodone Bitartrate and Acetaminophen Tablets USP, (7.5 mg/500 mg, 10 mg/500 mg)
74-184/S-006	Methadose Dispersible Tablets (Methadone Hydrochloride tablets USP, 40 mg)
89-160/S-040	ANEXIA Hydrocodone Bitartrate and Acetaminophen Tablets USP, (5 mg/500mg)
89-725/S-036	Hydrocodone Bitartrate and Acetaminophen Tablets USP, (7.5 mg/650 mg)

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-084/S-001; S-002; S-003; S-
004; S-005; S-006; S-007; S-008;
S-009; S-010; S-011; S-012; S-013;
S-014; S-015; S-016; S-017; S-018;
S-019; S-020; S-021; S-022; S-023;
S-024; S-028**

**BIOEQUIVALENCE
REVIEW(S)**

**Hydrocodone Bitartrate &
Acetaminophen Tablets, USP**

7.5 mg/750 mg, 10 mg/650 mg & 10 mg/660 mg

ANDA #40-084 / SC 11

Reviewer: Carol Y. Kim

x:\new\firm\firm\mallinck\ltrs&rev\40084DW.698.doc

Mallinckrodt Inc.

St. Louis, MO

Submission Date:

June 30, 1998

September 29, 1998

SUPPLEMENTAL AND AMENDMENT REVIEW

I. Background

1. The firm submitted this Supplement to provide the changes for a new manufacturer, formulation, and manufacturing process. Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg) will be manufactured, processed, and released by Mallinckrodt Inc. at Mallinckrodt's facility in Hobart, New York. Currently, King Pharmaceuticals, Inc. manufactures these products for Mallinckrodt Inc.
2. In December 1995, Mallinckrodt Chemical, Inc. purchased ANDA #40-084 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/750 mg), from King Pharmaceuticals, Inc. On July 29, 1996, Mallinckrodt Inc. received approval for Supplements S-001 and S-002 for an additional strength for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/660 mg). On October 16, 1996, Mallinckrodt received approval for Supplements S-007 and S-008 for an additional strength for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/650 mg).
3. The drug product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".
4. In support of the waiver request, the firm has submitted comparative formulation data and *in vitro* multi-point dissolution testing for the proposed drug products versus Mallinckrodt's currently marketed products manufactured by King Pharmaceuticals, Inc.

II. Formulation Comparison

Comparison of Proposed and Currently Marketed Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg (Unit Composition)

Strength	7.5 mg/750 mg		10 mg/650 mg		10 mg/660 mg	
Ingredients	Current formulation	Proposed formulation	Current formulation	Proposed formulation	Current formulation	Proposed formulation
Hydrocodone Bitartrate USP	7.5 mg	7.500 mg	10.0 mg	10.000 mg	10 mg	10.000 mg
Acetaminophen USP	750 mg	-	650 mg	-	660 mg	-
Magnesium Stearate NF						
Pregelatinized Starch NF						
Microcrystalline Cellulose NF						
Silicon Dioxide NF						
Stearic Acid NF						
Total	925.0 mg		825.0 mg		837.0 mg	

^ see Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 7.5 mg/500 mg and 10 mg/500 mg, ANDA 40-155)

^ Equivalent to current formulation's Acetaminophen 750 mg, 650 mg, and 660 mg as base per tablet at 100% potency (theoretical equivalent of Acetaminophen is 750 mg). This weight will be further adjusted upon the results of the potency test.

Composition of [redacted] for 7.5 mg/750 mg, 10mg/650 mg and 10 mg/660 mg

Ingredient	Weight per Individual Tablet
[redacted]	

III. Dissolution

The firm has submitted dissolution data for its drug product, Hydrocodone Bitartrate and Acetaminophen Tablets, USP, (7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg), applying the following conditions:

I. Conditions for Dissolution Testing

Method of dissolution	USP 23, Apparatus II (paddle)
Time/ Speed	30 minutes/ 50 rpm
No. of Units Tested	12
Medium	Phosphate Buffer, pH 5.8
Temperature	37°C
Volume	900 ml
Specifications	NLT 80% (Q) is dissolved in 30 minutes
Assay Methodology	
Reference Product	King Pharmaceuticals, Inc.'s Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg

II. Results of In Vitro Dissolution Testing

Sampling Times (minutes)	Current Product*: Hydrocodone Bitartrate Lot # HN7524 Strength: 7.5 mg/750 mg			Proposed Product@: Hydrocodone Bitartrate Lot # MHSC9726 Strength: 7.5 mg/750 mg			Current Product*: Acetaminophen Lot # HN7524 Strength: 10 mg/650 mg			Proposed Product@: Acetaminophen Lot # MHSC9726 Strength: 10 mg/650 mg		
	Mean %	Range	%CV	Mean %	Range	%CV	Mean %	Range	%CV	Mean %	Range	%CV
5	93.9		3.5	99.7		3.9	76.1		5.2	96.4		3.4
10	97.6		3.4	99.9		1.8	88.5		3.5	97.8		1.3
20	97.8		2.0	99.3		1.4	94.5		1.9	97.0		1.3
30	97.2		1.8	98.5		1.3	94.7		1.6	96.2		1.3

Sampling Times (minutes)	Current Product*: Hydrocodone Bitartrate Lot # HM7320 Strength: 10 mg/650 mg			Proposed Product@: Hydrocodone Bitartrate Lot #MHSC9805 Strength: 10 mg/650 mg			Current Product*: Acetaminophen Lot # HM7320 Strength: 10 mg/650 mg			Proposed Product@: Acetaminophen Lot # MHSC9805 Strength: 10 mg/650 mg		
	Mean %	Range	%CV	Mean %	Range	%CV	Mean %	Range	%CV	Mean %	Range	%CV
5	97.0		2.5	97.4		4.0	85.1		3.6	94.7		4.8
10	98.5		1.1	98.8		1.1	92.6		1.1	97.5		1.1
20	97.2		1.3	98.0		1.1	96.2		1.0	98.4		0.8
30	96.6		1.2	97.1		1.0	96.2		1.0	97.5		0.8

Sampling Times (minutes)	Current Product*: Hydrocodone Bitartrate Lot # HS7611 Strength: 10 mg/660 mg			Proposed Product@: Hydrocodone Bitartrate Lot # MHSC9807 Strength: 10 mg/660 mg			Current Product*: Acetaminophen Lot # HS7611 Strength: 10 mg/660 mg			Proposed Product@: Acetaminophen Lot # MHSC9807 Strength: 10 mg/660 mg		
	Mean %	Range	%CV	Mean %	Range	%CV	Mean %	Range	%CV	Mean %	Range	%CV
5	91.3		4.8	95.5		1.4	76.4		6.4	94.6		2.7
10	98.1		1.1	96.2		1.5	92.0		1.8	98.7		0.8
20	97.4		1.0	95.1		1.6	96.3		1.1	98.2		0.7
30	96.5		1.0	94.1		1.6	96.3		1.1	97.3		0.7

*Hydrocodone Bitartrate and Acetaminophen Tablets, USP, manufactured by King Pharmaceuticals, Inc.

@ Hydrocodone Bitartrate and Acetaminophen Tablets, USP, manufactured by Mallinckrodt Inc.

IV. Comments

1. Mallinckrodt Inc.'s dissolution data for the Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg are acceptable.
2. The drug product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".
3. The change in the composition of inactive ingredients for the proposed drug products does not pose questions of safety or effectiveness.
4. [redacted] has been previously accepted by DBE, ANDA #40-201, ANDA #40-155 (approval dated April 14, 1997). The composition of [redacted] is listed in DMF [redacted].
5. Although the amounts of Acetaminophen in [redacted] for all strengths are [redacted] 750 mg vs. [redacted], 650 mg vs. [redacted], 660 mg vs. [redacted] than the current formulation, the proposed formulations are equivalent, respectively, based on [redacted] per tablet at 100% potency (theoretical equivalent of Acetaminophen is [redacted]). Also, based on USP 23 specifications, Hydrocodone Bitartrate and Acetaminophen Tablets should contain the equivalent of not less than 90.0% and not more than 110.0% of the labeled amounts of Hydrocodone Bitartrate and Acetaminophen Tablets.
6. The waivers of in vivo bioequivalence study requirements may be granted based on 21 CFR 320.22 (c).

V. Recommendation

1. The dissolution testing data conducted by Mallinckrodt Inc., on its drug product, Hydrocodone Bitartrate & Acetaminophen Tablets, 7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg , lot #MHSC9726, lot #MHSC9805, lot #MHSC9807, respectively, are acceptable.
2. The Division of Bioequivalence agrees that the information submitted by Mallinckrodt Inc. on its drug product, Hydrocodone Bitartrate & Acetaminophen Tablets, USP, 7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg falls under 21 CFR section 320.22 (c) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study requirements for the proposed products are granted.
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 phosphate buffer pH 5.8 at 37°C using USP 23 Apparatus II (paddle) at 50 rpm. The proposed product should meet the following specifications:

Not less than 80% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the recommendations.



Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

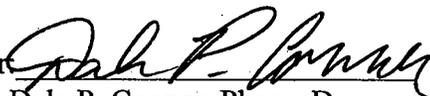
RD INITIALLED BY BDAVIT

FT INITIALLED BY BDAVIT

Bm Dated 10/1/98
Barbara M Daint

Date: 10/5/98

Concur



Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: 10/5/98

file 6

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #40-084 APPLICANT: Mallinckrodt, Inc.
S-011

DRUG PRODUCT: Hydrocodone Bitartrate & Acetaminophen
Tablets, USP, 7.5 mg/750mg, 10 mg/650mg, 10 mg/660mg

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,



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

6

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 40-084 / SC 11

SPONSOR: Mallinckrodt, Inc.

DRUG & DOSAGE FORM: Hydrocodone Bitartrate & Acetaminophen Tablets, USP

STRENGTH (S): 7.5 mg/750mg, 10 mg/650 mg & 10 mg/660 mg

TYPE OF STUDY: SD SDF MULT OTHER X

STUDY SUMMARY: N/A

Formulation is acceptable, waiver is granted

PRIMARY REVIEWER: Carol Y. Kim

BRANCH: 3
DATE: 10/2/98

INITIAL: Carol Y. Kim

TEAM LEADER: Barbara M. Davit

BRANCH: 3
DATE: 10/5/98

INITIAL: B M Davit

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: BTM DATE: 10/5/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: _____ DATE: _____

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-084/S-001; S-002; S-003; S-004;
S-005; S-006; S-007; S-008; S-009;
S-010; S-011; S-012; S-013; S-014;
S-015; S-016; S-017; S-018; S-019;
S-020; S-021; S-022; S-023; S-024;
S-028**

**ADMINISTRATIVE
DOCUMENTS**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT

MALLINCKRODT INC.

DATE OF SUBMISSION

December 16, 2003

TELEPHONE NO. (Include Area Code)

(314) 654-6258

FACSIMILE (FAX) Number (Include Area Code) (314) 654-6496

APPLICANT ADDRESS (Number, Street, City, State, ZIP Code or Mail Code, and U.S. License number if previously issued):

675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134-0840

AUTHORIZED U.S. AGENT NAME AND ADDRESS (Number, Street, City, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) ANDA 40-084

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Hydrocodone Bitartrate and Acetaminophen Tablets, USP

PROPRIETARY NAME (trade name) IF ANY

ANEXSIA®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5); 4'-hydroxyacetanilide

CODE NAME (If any)

DOSAGE FORM:

Tablets

STRENGTHS: 7.5 mg/750 mg, 10 mg/650 mg, 10 mg/660 mg

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE: For the relief of moderate to moderately severe pain

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Vicodin ES

Holder of Approved Application

Knoll Laboratories

TYPE OF SUBMISSION

(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION PAS FOR THE

DURING

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 (one)

THIS APPLICATION IS:

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Not Applicable

DEC 17 2003

OGD/CDEH

This application contains the following items: (Check all that apply)

	1. Index
	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S. c 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

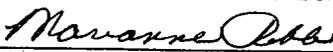
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions on the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local state and Federal environmental impact laws

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Marianne Robb, Manager, Official Correspondent	DATE 12/16/2003
ADDRESS (Street, City, State and ZIP Code) 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134-0840		Telephone Number (314) 654- 6258

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

Establishment Information

1. Full Address of the facility for the manufacturing, processing, testing, stability, packaging and labeling, release, holding and distribution of the drug product is Mallinckrodt Inc., 172 Railroad Avenue, P.O. Box P, Hobart, NY 13788, Establishment Registration 1317295 (CFN), Contact: James Allen (607) 538-9124, Ext. 3009.

Process	Commercial Batches	
	Building	Alternate
Vault Storage Raw Material	12b	1, 16
Dispensing, Tableting, Manufacturing, Inspection, Bulk Packaging	12a	
Packaging, _____	12a	12
Raw Material Sampling, In-Process Testing Laboratory, Batch Record Review	12a	
Warehouse - Receipt/Hold/Quarantine	12, 12b	16
Warehouse - Raw Material Release	12b	16
Bottle Packaging	12c	
Finished Product Storage	16	12b
Distribution	9	
Stability Samples Storage	12a	
Release and Stability Testing	12a	

2. Full Address of the Manufacturing and Control Site for Active Pharmaceutical Ingredient (Hydrocodone Bitartrate, USP) is Mallinckrodt Inc., 3600 North Second Street, St. Louis MO 63147, Contact: Patricia Benson (314) 654-0482, Establishment Registration 1940521 (CFN).

3.

[Redacted area with a signature 'j/IS' visible]

4. Contract Facilities

[Redacted area]

APPEARS THIS WAY
ON ORIGINAL

SUMMARY

- ANDA 40-050:** Methadose® Oral Tablets (Methadone Hydrochloride Tablets, USP)
(5 mg and 10 mg)
- ANDA 40-084:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg)
- ANDA 40-201:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/500 mg and 10 mg/500 mg)
- ANDA 40-300:** Methylin® Methylphenidate Hydrochloride Tablets, USP
(5 mg, 10 mg, and 20 mg)
- ANDA 40-400:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/325 mg)
- ANDA 40-405:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/325 mg)*
- ANDA 40-409:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5 mg/325 mg)*
- ANDA 74-184:** Methadose® Dispersible Tablets (Methadone Hydrochloride Tablets, USP)
(40 mg)
- ANDA 75-629:** Methylin® ER (methylphenidate HCl extended-release tablets, USP)
(10 mg and 20 mg)
- ANDA 75-738:** Propoxyphene Napsylate and Acetaminophen Tablets, USP (100 mg/650 mg)
- ANDA 89-160:** ANEXSIA® hydrocodone bitartrate and acetaminophen tablets, USP
5 mg/500 mg*
- ANDA 89-725:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/650 mg)*

* Hydrocodone Bitartrate and Acetaminophen, Tablets USP (5 mg/500 mg, 7.5 mg/325 mg and 7.5 mg/650 mg) may also be marketed under the proprietary name, ANEXSIA®.

Mallinckrodt Inc. hereby submits these Supplemental Applications for Prior Approval under 21 C.F.R. § 314.70(b) for the above referenced applications. These products are manufactured, processed, packaged, labeled, tested for release and stability, held and distributed by Mallinckrodt Inc. at Mallinckrodt's facility in Hobart, New York.

These supplemental applications provide for _____ Process validation has
as an approved in-process control during _____



**APPEARS THIS WAY
ON ORIGINAL**

No other changes are proposed for the Chemistry, Manufacturing and Controls for this product. Revised batch records that _____ during _____ and include this testing only at initiation of the _____ will be filed with the next annual report for each product.

For ease of reference, the supplemental application is numbered sequentially in the bottom right corner so that both text and attachments bear consecutive numbering. Three copies of the amendment are filed: an archival copy (in a blue folder), a technical review copy (in a red folder), and field copy (in a maroon folder). The technical review copy and the field copy are identical to the archival copy and a certification attesting to this is provided in the Field Copy Certification.

**APPEARS THIS WAY
ON ORIGINAL**

**SUPPLEMENTAL APPLICATION FOR PRIOR APPROVAL
FIELD COPY CERTIFICATION**

Mallinckrodt Inc. hereby certifies that pursuant to 21 C.F.R. §314.94(d)(5) a field copy of this Prior Approval Supplemental Application for ANDA 40-084: Hydrocodone Bitartrate and Acetaminophen tablets, USP (7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg) has been prepared and submitted to the District Office in Buffalo, concurrently with the archival and review copies. This field copy contains a true and accurate copy of the information prepared to satisfy requirements of technical Section 21 C.F.R. §314.94(a)(9) contained in the archival and review copies of this supplemental application.

Marianne Robb

Marianne Robb
Official Correspondent

December 8, 2003

Date

Telephone Conversation Memorandum

ANDA: 40-084/S-010, 011, 012, 013, 014, 015

DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets

FIRM: Mallinckrodt

PERSONS INVOLVED: Mariaanne Robb, Jim Allen, Jeen Min

PHONE NUMBER: 314-654-6258

DATE: 15-OCT-1999

Conversation:

Q: Mallinckrodt asked if the hardness specification is an issue with the reviewer.

A: We will deal with the hardness issue once the reviewer looks at the application in a couple of days.

Jeen Min, R. Ph.
Project Manager, Div Chem II, Team 9, OGD

Jeen Min 10/21/99

Attachment: Electronic mail message

From - Jim Allen
To - Jeen Min
Dated - 10/15/99

Cc: ANDA 40-084
Division file (1)

File: V:\FIRMSAMMALLINCKRODT\TELECONS\40084S010 HARDNESS.DOC

Electronic Mail Message

Date: 10/15/99 9:52:59 AM
From: Allen, Jim M (Jim.M.Allen@MKG.com)
To: 'minj@cder.fda.gov' (minj@Al)
Cc: Haag, Tom (Tom.Haag@MKG.com)
Cc: Lake, Bob S (Bob.Lake@MKG.com)
Cc: Robb, Marianne (Marianne.Robb@MKG.com)
Subject: ANDA 40-084 Hydrocodone Bitartrate and Acetaminophen Tablets USP 7.5/75

The Mallinckrodt Inc. manufacturing site located in Hobart, NY is currently undergoing a PAI for ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen Tablets USP (7.5/750, 10/650 and 10/660): S-010, S-011, S-012, S-013, S-014, S-015.

Peg Sarles, the FDA Investigator from the Albany NY Office, expressed concern about the final release and stability hardness specification that is listed in the pending supplement. Peg informed us that she spoke to the reviewer of this ANDA on Wednesday, October 13, 1999. On Thursday, October 14, 1999 she told us this issue would be handled by the reviewing chemist in the Division of Generic Drugs.

Our questions are:

- * Is this hardness specification an issue with the reviewer?
- * If this is an issue, we are prepared to immediately file an amendment to this application. How will this amendment affect the review of our response dated May 28, 1999 which we understand is currently with the reviewer? Should we provide a "desk copy" of this new amendment to the reviewer?

Jim Allen

**APPEARS THIS WAY
ON ORIGINAL**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: ANDA 40084/010	Priority:	Org Code: 600
Stamp: 01-JUL-1998 Regulatory Due:	Action Goal:	District Goal: 01-DEC-1998
Applicant: MALLINCKRODT CHEM 16305 SWINGLEY RIDGE DR CHESTERFIELD, MO 63017	Brand Name:	Established Name: HYDROCODONE BITARTRATE;ACETAMINOPHEN
	Generic Name:	
	Dosage Form: TAB (TABLET)	
	Strength: 7.5MG/750MG,5.0MG/500MG	
FDA Contacts: T. AMES (HFD-640)	301-827-5849	, Project Manager
M. SELVAM (HFD-647)	301-827-5859	, Review Chemist

Overall Recommendation:

ACCEPTABLE on 04-NOV-1999 by S. ADAMS (HFD-320) 301-594-0095

ACCEPTABLE on 03-AUG-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1317295 MALLINCKRODT CHEMICAL INC 58 PEARL ST HOBART, NY 13788	DMF No: AADA No:
Profile: TCM OAI Status: NONE	Responsibilities: FINISHED DOSAGE
Last Milestone: OC RECOMMENDATION	MANUFACTURER
Milestone Date: 05-AUG-1999	FINISHED DOSAGE RELEASE
Decision: ACCEPTABLE	TESTER
Reason: DISTRICT RECOMMENDATION	

Establishment: 1319618 MALLINCKRODT CHEMICAL INC 13 RAILROAD AVE HOBART, NY 13788	DMF No: AADA No:
Profile: TCM OAI Status: NONE	Responsibilities: FINISHED DOSAGE
Last Milestone: OC RECOMMENDATION	MANUFACTURER
Milestone Date: 04-NOV-1999	FINISHED DOSAGE RELEASE
Decision: ACCEPTABLE	TESTER
Reason: DISTRICT RECOMMENDATION	

Establishment: 1319687 MALLINCKRODT CHEMICAL INC 18 CORNELL AVE HOBART, NY 13788	DMF No: AADA No:
Profile: TCM OAI Status: NONE	Responsibilities: FINISHED DOSAGE PACKAGER
Last Milestone: OC RECOMMENDATION	
Milestone Date: 04-NOV-1999	

FDA ORDER LBS
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: _____

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: _____

Establishment: _____

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **05-AUG-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: _____

**APPEARS THIS WAY
ON ORIGINAL**

RECORD OF TELEPHONE CONVERSATION

I spoke with Thomas Rogers (King Pharmaceuticals) and Mary Ann Robbck Smith (Mallinkrodt Chemical) 3-5-96 and relayed the labeling deficiencies of ANDA 40-084/S-006 to them (see review dated 2-15-96) and suggested that they submit FPL labels and labeling as a telephone amendment to this supplement. I also related to them our general policy on the location of the asterisk in controlled substance labels and labeling. They agreed to do the above as soon as possible.

**APPEARS THIS WAY
ON ORIGINAL**

DATE March 5, 1996										
ANDA NUMBER 40-084/S-006										
IND NUMBER										
TELECON										
<table border="0"> <tr> <td>INITIATED BY</td> <td>MADE</td> </tr> <tr> <td>APPLICANT/</td> <td>X BY</td> </tr> <tr> <td>SPONSOR</td> <td>TELE.</td> </tr> <tr> <td>X FDA</td> <td>_ IN</td> </tr> <tr> <td></td> <td>PERSON</td> </tr> </table>	INITIATED BY	MADE	APPLICANT/	X BY	SPONSOR	TELE.	X FDA	_ IN		PERSON
INITIATED BY	MADE									
APPLICANT/	X BY									
SPONSOR	TELE.									
X FDA	_ IN									
	PERSON									
PRODUCT NAME Hydrocodone Bitartate/APAP tablets										
FIRM NAME King Pharm. Mallinkrodt										
NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Thomas Rogers (Dir. Reg. Affairs) Mary Ann Robb										
TELEPHONE NUMBER (423) 989-8172 (King Pharm.) (314) 530-2128 (Mallinkrodt)										
SIGNATURE Adolph Vezza <i>Adolph Vezza 3/5/96</i>										

Division of Labeling + Program Support

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

J

REQUEST TYPE (Check One) <input checked="" type="checkbox"/> Original <input type="checkbox"/> FollowUp <input type="checkbox"/> FUR	DATE 5.22.96	PHONE NO. (301)594-0305	EER ID # 10355
REQUESTORS NAME: Ubrani V. Venkataram	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-647
APPLICATION AND SUPPLEMENT NUMBER: ANDA 40-084/S-007			
BRAND NAME: None	ESTABLISHED NAME: Hydrocodone Bitartrate and Acetaminophen		
DOSAGE STRENGTH: 5 mg/500 mg , 7.5 mg/750 mg & 10 mg/650 mg			STERILE <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No ~
PROFILE CLASS: TCM	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)		
APPLICANT'S NAME: King Pharmaceuticals, Inc. (Formerly RSR Laboratories)			
APPLICANT'S ADDRESS: 501-551 Fifth Street, Bristol, TN 37620			
COMMENTS : Additional manufacturing facility			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

RESPONSIBILITY

DMF NUMBER/
PROFILE CODE

FKEY CIRTS ID

HFD-324 USE ONLY ~

(Name and Complete Address)	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY ~
[] [] []		DMF - SHAC NEE TCM		AC 12/20/94
3.				
4.				
APPEARS THIS WAY ON ORIGINAL				
5.				

FOR HFD-324 USE ONLY:	CSO Jannie Dambrosio	DATE RECEIVED 6/4/96
	CGMP COMPLIANCE STATUS Acceptable	DATE 6/5/96

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**40-084/S-001; S-002; S-003; S-004;
S-005; S-006; S-007; S-008; S-009;
S-010; S-011; S-012; S-013; S-014;
S-015; S-016; S-017; S-018; S-019;
S-020; S-021; S-022; S-023; S-024;
S-028**

CORRESPONDENCE

TELEPHONE AMENDMENT

July 30, 2004

SUPPLEMENT AMENDMENT
SCA-025-AC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**RE: ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen Tablets
7.5 mg/750 mg**

Dear Mr. Smith:

Mallinckrodt Inc. hereby submits this Telephone Amendment to the Special Supplement -- Changes Being Effected in 30 days which affected 9 ANDAs. The CBE-30 provided for the addition of a new bulk package container/closure system.

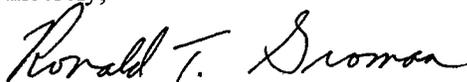
As requested by Glen Smith, Lead Chemist FDA OGD Division of Chemistry II, to Ronald T. Groman, Tyco-Healthcare -- Mallinckrodt, on July 27, 2004, a commercial stability commitment indicating one production lot per year will be placed on stability at controlled room temperature conditions 25°+2°C/60%+5% RH. The agency will receive an original Telephone Amendment for each ANDA number listed on the attached page.

The archival copy of this amendment consists of one (1) volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder.

This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this amendment, a true copy of the technical sections of the amendment was sent to the District Office in Buffalo, NY and the District Office in Parsippany, NJ. These "field copies" are contained in maroon folders.

Correspondence related to this submission should be addressed to Ronald T. Groman, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6060 or call Dr. James F. Baker, PhD., Director of Clinical and Regulatory Affairs at 314-654-5729.

Sincerely,



Ronald T. Groman,
Manager, Regulatory Affairs
FAX: 314-654-6496

RECEIVED
AUG 03 2004
OGD / CDER

July 26, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

SUPPLEMENT AMENDMENT
SCB-028-AC

RE: ANDA # 40-084 Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg

Mallinckrodt Inc. hereby submits this Telephone Amendment to the Special Supplement-Changes Being Effected- 30 days submitted on June 30, 2004 which affected 33 ANDAs and on July 1, 2004 which affected 3 ANDAs. The CBE-30 provided for the transfer of laboratory testing sites from _____ to Corporate Laboratory Science Center, a Tyco Healthcare facility.

As requested by Ted Palat, Project Manager FDA OGD Division of Chemistry II, to Ronald T. Groman, Tyco Healthcare -- Mallinckrodt, on July 22, 2004, a post approval commitment relating to test methods has been provided herein. The agency will receive an original Telephone Amendment for each ANDA number listed on the attached page.

The archival copy of this amendment consists of one (1) volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder.

This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this amendment, a true copy of the technical sections of the amendment was sent to the District Office in Buffalo, NY and the District Office in Parsippany, NJ. These "field copies" are contained in maroon folders.

Correspondence related to this submission should be addressed to Ronald T. Groman, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6060 or call Dr. James F. Baker, PhD., Director of Clinical and Regulatory Affairs at 314-654-5729.

Sincerely,



Ronald T. Groman,
Manager, Regulatory Affairs
FAX: 314-654-6496

RECEIVED
JUL 28 2004
OGD/ODER

**SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED-30 DAYS
CHANGES TO ANALYTICAL LABORATORY FOR SET OF SUPPLEMENTS**

June 30, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA NO. 40-084 REF. NO. SCB-028-AT
NDA SUPPL FOR facility-add

RE: ANDA # 40-084 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg)

Dear Madame or Sir:

Mallinckrodt Inc. hereby submits this Special Supplemental-Changes Being Effected -30 days under 21 C.F.R. § 314.70(c) for the above referenced application. This submission is being submitted in accordance with the Guidance for Industry "Changes to an Approved NDA or ANDA" Revision 1 Section VI. C. 1. d. Mallinckrodt intends to proceed with the distribution of this material within 30 days of the date of this submission (July 30, 2004) unless otherwise directed by FDA.

This supplemental application provides for the transfer of contract laboratory services from _____ to Corporate Laboratory Science Center, a Tyco Healthcare facility. The attached list outlines multiple ANDAs and NDAs affected by this change; therefore, the listed supplements are being submitted concurrently for review. The agency will receive an original supplement for each ANDA or NDA number listed on the attached page.

The archival copy of this supplement consists of one (1) volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this Supplemental Application for Changes Being Effected-30 days, a true copy has been sent to the District Office in Buffalo, NY and the District Office in Maitland, FL. These "field copies" are contained in maroon folders. Please refer to "Executive Summary" which is included immediately following the Table of Contents for a detailed list of applications affected by this supplemental application.

Correspondence related to this submission should be addressed to Ronald T. Groman, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6060 or James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,



Ronald T. Groman
Manager, Regulatory Affairs
FAX: 314-654-6496

RECEIVED
JUL 01 2004
OGD/CDER
RECEIVED
JUL 01 2004
OGD/CDER

allinckrodt

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED
CBE-0

June 24, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA NO. 40-084 REF NO. S-029/AT
ANDA SUPPL FOR Control Rev.

ANDA 40-084: ANEXSIA® hydrocodone bitartrate and acetaminophen tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg)

Dear Madame or Sir:

Mallinckrodt Inc. hereby submits this under 21 C.F.R. § 314.70(c)(1) for the above referenced products that are manufactured, processed, packaged, labeled, tested for release and stability, held and distributed by Mallinckrodt Inc. at Mallinckrodt's facility in Hobart, New York.

This supplemental application provides for a tightening of the hardness specification for release and stability.

The archival copy of this Special Supplement – Changes Being Effectuated (CBE-0) consists of one (1) volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder.

This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this Supplemental Application for Prior Approval, a true copy has been sent to the District Office in Buffalo, NY. This "field copy" is contained in a maroon folder. For more detailed information on the organization of this supplemental application, please refer to "Executive Summary".

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6258 or James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,

Marianne Robb

Marianne Robb
Official Correspondent
FAX: 314-654-6496

RECEIVED
JUN 25 2004
OGD / CDER

SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED-30 DAYS

June 9, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA NO. 40084 REF NO. SCA-025AT
NDA SUPPL FOR PACKAGING ADD

NDA NO. 40084 REF NO. SL-026AT
NDA SUPPL FOR LABELING REV

**RE: ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen
Tablets, USP 7.5 mg/750 mg**

Dear Madam or Sir:

In accordance with the Guidance for Industry "Changes to an Approved NDA or ANDA" section IX. C. 1. a., Mallinckrodt Inc. is submitting a Special Supplement-Changes Being Effected-30 Days for ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen Tablets, USP 7.5 mg/750 mg. This CBE-30 supplemental application provides for the addition of a new bulk packaging container/closure system. Mallinckrodt intends to proceed with this change within 30 days of the date of this submission unless otherwise directed by FDA.

Stability data has been provided for the new bulk container. Also, information on the new container/closure configurations has been provided.

The bulk container labeling is supplied in this application.

The archival copy of this supplemental application consists of one (1) volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. This also certifies that, per 21C.F.R. §314.440(a)(4) and concurrently with the filing of this CBE-30, a true copy of the technical sections of the special supplement was sent to the

RECEIVED

JUN 14 2004

OGD / CDER

District Offices in Buffalo, NY. This "field copy" is contained in a maroon folder. For more detailed information on the organization of this application, please refer to "Executive Summary" which is included immediately following the Table of Contents.

Correspondence related to this submission should be addressed to Ronald T. Groman, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6060 or call Dr. James F. Baker, PhD., Director of Clinical and Regulatory Affairs at 314-654-5729.

Sincerely,

A handwritten signature in black ink that reads "Ronald T. Groman". The signature is written in a cursive style with a large initial 'R'.

Ronald T. Groman
Manager, Regulatory Affairs
FAX: 314-654-6496

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

SUPPLEMENTAL APPLICATION FOR PRIOR APPROVAL

December 16, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA NO ~~40-084~~ TEF NO ~~905-024~~
NDA SUPPL FOR Control Rev

- RE: ANDA 40-050:** Methadose® Oral Tablets (Methadone Hydrochloride Tablets, USP)
(5 mg and 10 mg)
- ANDA 40-084:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg)
- ANDA 40-201:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/500 mg and 10 mg/500 mg)
- ANDA 40-300:** Methylin® Methylphenidate Hydrochloride Tablets, USP
(5 mg, 10 mg, and 20 mg)
- ANDA 40-400:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/325 mg)
- ANDA 40-405:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/325 mg)
- ANDA 40-409:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5 mg/325 mg)
- ANDA 74-184:** Methadose® Dispersible Tablets (Methadone Hydrochloride Tablets, USP)
(40 mg)
- ANDA 75-629:** Methylin® ER (methylphenidate HCl extended-release tablets, USP)
(10 mg and 20 mg)
- ANDA 75-738:** Propoxyphene Napsylate and Acetaminophen Tablets, USP (100 mg/650 mg)
- ANDA 89-160:** ANEXSIA® hydrocodone bitartrate and acetaminophen tablets, USP
(5 mg/500 mg)
- ANDA 89-725:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/650 mg)

Dear Madame or Sir:

Mallinckrodt Inc. hereby submits these Supplemental Applications for Prior Approval under 21 C.F.R. § 314.70(b) for the above referenced products that are manufactured, processed, packaged, labeled, tested for release and stability, held and distributed by Mallinckrodt Inc. at Mallinckrodt's facility in Hobart, New York.

These supplemental applications provide for _____

The archival copy of this original application consists of one (1) volume. An archival copy is being

RECEIVED

DEC 17 2003

OGD/CDEF

filed in a blue folder and a technical review copy is being filed in a red folder.

This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this Supplemental Application for Prior Approval, a true copy has been sent to the District Office in Buffalo, NY. This "field copy" is contained in a maroon folder. For more detailed information on the organization of this supplemental application, please refer to "Executive Summary".

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6258 or James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,



Marianne Robb
Official Correspondent
FAX: 314-654-6496

**APPEARS THIS WAY
ON ORIGINAL**

SUPPLEMENTAL APPLICATION FOR PRIOR APPROVAL - FIELD COPY

December 16, 2003

John A. Posadowski
Pre-Approval Manager, Buffalo, New York District Office
Food and Drug Administration
Olympic Towers, Suite 100
300 Pearl Street
Buffalo, New York 14202

- RE: ANDA 40-050:** Methadose® Oral Tablets (Methadone Hydrochloride Tablets, USP)
(5 mg and 10 mg)
- ANDA 40-084:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg)
- ANDA 40-201:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/500 mg and 10 mg/500 mg)
- ANDA 40-300:** Methylin® Methylphenidate Hydrochloride Tablets, USP
(5 mg, 10 mg, and 20 mg)
- ANDA 40-400:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/325 mg)
- ANDA 40-405:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/325 mg)
- ANDA 40-409:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5 mg/325 mg)
- ANDA 74-184:** Methadose® Dispersible Tablets (Methadone Hydrochloride Tablets, USP)
(40 mg)
- ANDA 75-629:** Methylin® ER (methylphenidate HCl extended-release tablets, USP)
(10 mg and 20 mg)
- ANDA 75-738:** Propoxyphene Napsylate and Acetaminophen Tablets, USP (100 mg/650 mg)
- ANDA 89-160:** ANEXSIA® hydrocodone bitartrate and acetaminophen tablets, USP
(5 mg/500 mg)
- ANDA 89-725:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/650 mg)

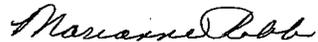
Dear Sir:

Per 21 C.F.R. § 314.440(a)(4) Mallinckrodt Inc. has concurrently submitted Supplemental Applications for Prior Approval for the above referenced applications. These supplemental applications provide for _____

These supplemental applications, which have been submitted to CDER in Rockville, Maryland, are also provided in maroon folders to the District Office in Buffalo, New York. This field copy of each application consists of one (1) volume. For more detailed information on the organization of this application, please refer to the "Executive Summary".

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6258 or call James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,



Marianne Robb
Official Correspondent
Fax: 314-654-6496

APPEARS THIS WAY
ON ORIGINAL

SUPPLEMENTAL APPLICATION FOR PRIOR APPROVAL

October 27, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA NO. 40-084 REF NO. **SCD-028**
NDA SUPPL FOR - Central Rev

- RE: ANDA 40-050:** Methadose® Oral Tablets (Methadone Hydrochloride Tablets, USP)
(5 mg and 10 mg)
- ANDA 40-084:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg)
- ANDA 40-201:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/500 mg and 10 mg/500 mg)
- ANDA 40-300:** Methylin® Methylphenidate Hydrochloride Tablets, USP
(5 mg, 10 mg, and 20 mg)
- ANDA 40-352:** Meperidine Hydrochloride Tablets, USP (50 mg and 100 mg)
- ANDA 40-400:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/325 mg)
- ANDA 40-405:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/325 mg)
- ANDA 40-409:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5 mg/325 mg)
- ANDA 40-419:** Acetaminophen and Codeine Phosphate Tablets, USP
(300 mg/15 mg, 300 mg/30 mg, and 300 mg/60 mg)
- ANDA 40-436:** Dextroamphetamine Sulfate Tablets, USP (5 mg and 10 mg)
- ANDA 74-184:** Methadose® Dispersible Tablets (Methadone Hydrochloride Tablets, USP)
(40 mg)
- ANDA 75-629:** Methylin® ER (methylphenidate HCl extended-release tablets, USP)
(10 mg and 20 mg)
- ANDA 75-738:** Propoxyphene Napsylate and Acetaminophen Tablets, USP (100 mg/650 mg)
- ANDA 75-983:** Tramadol Hydrochloride Tablets (50 mg)
- ANDA 89-160:** ANEXSIA® hydrocodone bitartrate and acetaminophen tablets, USP
(5 mg/500 mg)
- ANDA 89-725:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/650 mg)

Dear Madame or Sir:

Mallinckrodt Inc. hereby submits these Supplemental Applications for Prior Approval under 21 C.F.R. § 314.70(b) for the above referenced products that are manufactured, processed, packaged, labeled, tested for release and stability, held and distributed by Mallinckrodt Inc. at Mallinckrodt's facility in Hobart, New York.

OCT 28 2003

OGS/CSL

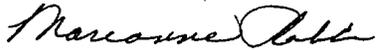
These supplemental applications provide for _____ as an approved in-process control.

The archival copy of this original application consists of one (1) volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder.

This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this Supplemental Application for Prior Approval, a true copy has been sent to the District Office in Buffalo, NY. This "field copy" is contained in a maroon folder. For more detailed information on the organization of this supplemental application, please refer to "Executive Summary."

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6258 or James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,



Marianne Robb
Official Correspondent
FAX: 314-654-6496

**APPEARS THIS WAY
ON ORIGINAL**

SUPPLEMENTAL APPLICATION FOR PRIOR APPROVAL - FIELD COPY

October 27, 2003

John A. Posadowski
Pre-Approval Manager, Buffalo, New York District Office
Food and Drug Administration
Olympic Towers, Suite 100
300 Pearl Street
Buffalo, New York 14202

- RE: ANDA 40-050:** Methadose® Oral Tablets (Methadone Hydrochloride Tablets, USP)
(5 mg and 10 mg)
- ANDA 40-084:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg)
- ANDA 40-201:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/500 mg and 10 mg/500 mg)
- ANDA 40-300:** Methylin® Methylphenidate Hydrochloride Tablets, USP
(5 mg, 10 mg, and 20 mg)
- ANDA 40-352:** Meperidine Hydrochloride Tablets, USP (50 mg and 100 mg)
- ANDA 40-400:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (10 mg/325 mg)
- ANDA 40-405:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/325 mg)
- ANDA 40-409:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5 mg/325 mg)
- ANDA 40-419:** Acetaminophen and Codeine Phosphate Tablets, USP
(300 mg/15 mg, 300 mg/30 mg, and 300 mg/60 mg)
- ANDA 40-436:** Dextroamphetamine Sulfate Tablets, USP (5 mg and 10 mg)
- ANDA 74-184:** Methadose® Dispersible Tablets (Methadone Hydrochloride Tablets, USP)
(40 mg)
- ANDA 75-629:** Methylin® ER (methylphenidate HCl extended-release tablets, USP)
(10 mg and 20 mg)
- ANDA 75-738:** Propoxyphene Napsylate and Acetaminophen Tablets, USP (100 mg/650 mg)
- ANDA 75-983:** Tramadol Hydrochloride Tablets (50 mg)
- ANDA 89-160:** ANEXSIA® hydrocodone bitartrate and acetaminophen tablets, USP
(5 mg/500 mg)
- ANDA 89-725:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/650 mg)

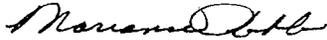
Dear Sir:

Per 21 C.F.R. § 314.440(a)(4) Mallinckrodt Inc. has concurrently submitted Supplemental Applications for Prior Approval for the above referenced applications. These supplemental applications provide for _____ as an approved in-process control.

These supplemental applications, which have been submitted to CDER in Rockville, Maryland, are also provided in maroon folders to the District Office in Buffalo, New York. This field copy of each application consists of one (1) volume. For more detailed information on the organization of this application, please refer to the "Executive Summary."

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6258 or call James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,



Marianne Robb
Official Correspondent
Fax: 314-654-6496

**APPEARS THIS WAY
ON ORIGINAL**

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED

June 26, 2003

Office of Generic Drugs - Division of Labeling and Program Support
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Fishers Document Room
5600 Fishers Lane
Rockville, MD 20852-1420

NDA NO. 40-084 REF NO. SL-022 *lan*
NDA SUPPL FOR Labeling Rev.

ANDA 40-084 HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
7.5 mg/750 mg, 10 mg/650 mg, 10 mg/660 mg
ANEXSIA® (hydrocodone bitartrate and acetaminophen tablets, USP)
10 mg/660 mg

Dear Sir or Madam:

Reference is made to the Agency's response letter of April 11, 2003 (copy included) for ANDA 40-084/S-020 regarding the addition of the contraindications and adverse reactions text to our insert as submitted September 24 2002.

The purpose of this supplement is to submit the labeling containing the requested additions:

- Statements for Geriatric Use to the four inserts
- Proprietary name requirements for 21 CFR 201.10(g)(1) to the Anexsia® insert
- Multiple strength statement to the Anexsia container labels

These changes in the package insert and container labels will be implemented at the next printing. In accordance with 21 CFR 314.70, twelve copies of final printed labeling and a side-by-side for each insert are provided. This labeling amendment consists of one (1) volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder.

Should you have any questions concerning this submission, please contact the undersigned at (314) 654-6255 by telephone or (314) 654-6496 by facsimile. In the event the undersigned is unavailable, please contact Celeste Reisch at (314) 654-3120 by telephone or (314) 654-6496 by facsimile.

Sincerely,

Russell D. Reed

Russell D. Reed
Labeling Manager

RECEIVED

JUN 30 2003

OGD/CDER

tyco
Healthcare

Mallinckrodt

Mallinckrodt Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Tele: 314 654-2000
www.mallinckrodt.com

ANDA NO. 40-084 REF NO. SCS-021
ANDA SUPPL FOR Control Rev.

SUPPLEMENTAL APPLICATION FOR PRIOR APPROVAL

November 20, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 40-084: ANEXSIA® hydrocodone bitartrate and acetaminophen tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg)

Dear Madame or Sir:

Mallinckrodt Inc. hereby submits this Supplemental Application for Prior Approval under 21 C.F.R. § 314.70(b). ANEXSIA® hydrocodone bitartrate and acetaminophen tablets, USP (7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg) is a Schedule III prescription drug indicated for the treatment of moderate to moderately severe pain. ANEXSIA® is manufactured, processed, packaged, labeled, tested for release and stability, held and distributed by Mallinckrodt Inc. at Mallinckrodt's facility in Hobart, New York.

This supplemental application provides for _____
testing as an approved in-process specification.

The archival copy of this original application consists of one (1) volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder.

RECEIVED

NOV 22 2002

OGD / CDER

This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this Supplemental Application for Prior Approval, a true copy has been sent to the District Office in Buffalo, NY. This "field copy" is contained in a maroon folder. For more detailed information on the organization of this supplemental application, please refer to "Executive Summary" which is included immediately following the Table of Contents.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6258 or James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,



Marianne Robb
Manager, Regulatory Submissions
FAX: 314-654-6496

**APPEARS THIS WAY
ON ORIGINAL**

tyco
Healthcare

RECEIVED

OCT 02 2002

MEGA/CDER

Mallinckrodt Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Tele: 314 654-2000
www.mallinckrodt.com

Mallinckrodt

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED

September 24, 2002

NDA 40-084, 10 mg/660 mg
NDA SUPPL FOR Labeling Rev. A1

Office of Generic Drugs - Division of Labeling and Program Support
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Fishers Document Room
5600 Fishers Lane
Rockville, MD 20852-1420

ANDA 40-084 HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
7.5 mg/750 mg, 10 mg/650 mg, 10 mg/660 mg
ANEXSIA® (hydrocodone bitartrate and acetaminophen tablets, USP)
10 mg/660 mg

Dear Sir or Madam:

Reference is made to the Agency's response letter of July 3, 2002 (copy included) for ANDA 40-468 regarding the addition of text to our insert labeling for previously approved applications of different strengths of Hydrocodone Bitartrate and Acetaminophen Tablets, USP.

The purpose of this supplement is to submit the labeling containing the requested additional statements:

- To The Contraindications Section -
Patients known to be hypersensitive to other opioids may exhibit cross-sensitivity to hydrocodone.
- To The Adverse Reactions Section -
Special Senses: Cases of hearing impairment or permanent loss have been reported predominantly in patients with chronic overdose.

This change in the package insert will be implemented at the next printing. In accordance with 21 CFR 314.70, 12 copies of final printed labeling are provided. This labeling amendment consists of one (1) volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder.

Should you have any questions concerning this submission, please contact the undersigned at (314) 654-6255 by telephone or (314) 654-6496 by facsimile. In the event the undersigned is unavailable, please contact Celeste Reisch at (314) 654-3120 by telephone or (314) 654-6496 by facsimile.

Sincerely,

Russell D. Reed

Russell D. Reed
Labeling Manager

*See the E-mail to Jean
on 10/23/02. Char
(filed in front of this letter)*

RECEIVED
OCT 02 2002
OGD / CDER

**RESPONSE TO A TELEPHONE AMENDMENT
FOR A PENDING SPECIAL SUPPLEMENT
CHANGES BEING EFFECTED - 30 DAYS**

August 26, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ATTENTION: CHAN PARK

**RE: ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/750 mg,
10 mg/650 mg, 10 mg/660 mg)**

Dear Mr. Park:

The following information is provided in response to your telephone request of August 26, 2002, in reference to a CBE-30 filed July 1, 2002. This CBE-30 included final printed bottle labeling as well as changes to the package insert for the above three strengths as requested in an April 2, 2002, deficiency notice.

As requested, this submission includes twelve copies of the package insert and accompanying side-by-side comparison for Hydrocodone Bitartrate and Acetaminophen Tablets, 10 mg/660 mg with all differences annotated and explained. For ease of reference, the original deficiency notice of April 2, 2002, and our cover letters of July 1, 2002, are also included.

Two copies of this amendment have been filed: an archival copy (in a blue folder), and a technical review copy (in a red folder). The technical review copy is identical to the archival copy.

Correspondence related to this submission should be addressed to Melissa Cay, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-3514 or call Ronald T. Groman., Manager, Regulatory Affairs at 314-654-6060.

Sincerely,



Melissa Cay
Senior Regulatory Affairs Associate
FAX: 314-654-6496

RECEIVED

AUG 28 2002

HFD-120/CDER

NDA SUPPL AMENDMENT
SLOI & AL

RECEIVED

AUG 30 2002

OGD / CDER

**RESPONSE TO A TELEPHONE AMENDMENT
FOR A PENDING SPECIAL SUPPLEMENT
CHANGES BEING EFFECTED - 30 DAYS**

July 24, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA SUPP AMEND
SCA-017-AM
SL-018-AM

RE: ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/750 mg, 10 mg/650 mg, 10 mg/660 mg)

Dear Sir or Madam:

The following information is provided in response to a telephone request of July 23, 2002, from the agency in reference to a CBE-30 filed July 1, 2002. This CBE-30 included final printed bottle labeling as well as changes to the package insert for the above three strengths as requested in an April 2, 2002, deficiency notice.

As requested, this submission includes twelve copies of the package insert and accompanying side-by-side comparison for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 mg/650 mg and 10 mg/660 mg with all differences annotated and explained. For ease of reference, the original deficiency notice of April 2, 2002, and our cover letters of July 1, 2002, are also included.

Three copies of this amendment have been filed: an archival copy (in a blue folder), a technical review copy (in a red folder), and a field copy (in a maroon folder). The technical review copy and field copy are identical to the archival copy as attested by the Field Copy Certification provided in this submission.

Correspondence related to this submission should be addressed to Melissa Cay, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-3514 or call Ronald T. Groman., Manager, Regulatory Affairs at 314-654-6060.

Sincerely,



Melissa Cay
Senior Regulatory Affairs Associate
FAX: 314-654-6496

RECEIVED

JUL 25 2002

OGD / CDER

**MINOR AMENDMENT TO A PENDING SUPPLEMENTAL APPLICATION
CHANGED BEING EFFECTED IN 30 DAYS**

July 1, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

SUPPL. AMENDMENT
SLO18 AM
SLO17 AM

RE: ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/750 mg, 10 mg/650 mg, 10 mg/660 mg)

Dear Sir or Madam:

The following information is provided in response to the April 2, 2002, request from the Agency in reference to the supplemental ANDA 40-084 as submitted on January 11, 2002. This amendment includes changes to the proposed package insert as requested by the Agency letter dated April 2, 2002. A side-by-side comparison for the package insert has been provided with all differences annotated and explained.

This change to the package insert moves the placement of "Meets USP Dissolution Test 1" to the Description section from the Storage Conditions section. This change will be implemented to package inserts for all hydrocodone bitartrate and acetaminophen tablet products and submitted either as a supplement or as part of the annual report.

No changes have been made to the bottle labeling. The bottle labeling is supplied in this amendment in final form.

Three copies of this amendment have been filed: an archival copy (in a blue folder), a technical review copy (in a red folder), and a field copy (in a maroon folder). The technical review copy and field copy are identical to the archival copy as attested by the Field Copy Certification provided in this submission.

RECEIVED
JUL 05 2002
OGD / CDER

ML
7/1/02

Correspondence related to this submission should be addressed to Melissa Cay, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-3514 or call James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,

A handwritten signature in black ink, appearing to read "Melissa Cay". The signature is fluid and cursive, with the first name "Melissa" being more prominent than the last name "Cay".

Melissa Cay
Senior Regulatory Affairs Associate
FAX: 314-654-6496

APPEARS THIS WAY
ON ORIGINAL

RECEIVED

JAN 14 2002

CDR/CDER

SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED-30 DAYS

January 11, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA NO. 40084 REF NO. SCA-017AT
NDA SUPPL FOR PACKAGING ADD
NDA NO. 40084 REF NO. SL-018AI
NDA SUPPL FOR LABELING REV

**RE: ANDA #40-084, Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg and 10 mg/660 mg)**

Dear Madam or Sir:

In accordance with the Guidance for Industry "Changes to an Approved NDA or ANDA", Mallinckrodt Inc. is submitting a Special Supplement-Changes Being Effected-30 Days for ANDA #40-084 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/750 mg, 10 mg/650 mg and 10 mg/660 mg). This CBE supplemental application provides for the addition of 30, 60, 90 and 120 count bottle sizes. Mallinckrodt intends to proceed with distribution of these new bottle sizes within 30 days of the date of this submission (February 11, 2002) unless otherwise directed by FDA.

Stability data has been provided for the 30 count bottle size exhibit batch. The 60 and 90 count bottles are bracketed within the 30 count bottle size and the currently approved 100 count bottle size. The 120 count bottle size is bracketed between the currently approved 100 and 500 count bottle sizes. Information on the new container/closure configurations has been provided.

The labeling provided in this application consists of four color proofs of bottle labeling and word processing files of the package insert. Final printed labeling is as yet unavailable from the labeling vendor. Final printed labeling will be provided in the next annual report. The final printed labeling will be identical to the labeling provided in this application.



The archival copy of this supplemental application consists of one (1) volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA was sent to the District Offices in Buffalo, NY. This "field copy" is contained in a maroon folder. For more detailed information on the organization of this application, please refer to "Executive Summary" which is included immediately following the Table of Contents.

Correspondence related to this submission should be addressed to Melissa Cay, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-3514 or call James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,

A handwritten signature in cursive script, appearing to read "Melissa Cay".

Melissa Cay
Senior Regulatory Affairs Associate
FAX: 314-654-6496

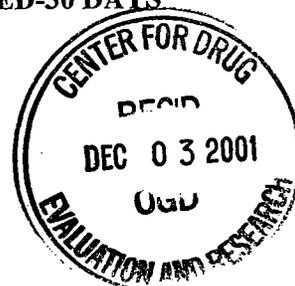
APPEARS THIS WAY
ON ORIGINAL

NDA NO. 40-084 REF. NO. SED-016 AT
NDA SUPPL FOR Package Addition

Mallinckrodt Inc.

675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134Phone: 314.654.2000
www.mallinckrodt.com**SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED-30 DAYS**

November 30, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773**RE: ANDA #40-084, Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 mg/650 mg**

Dear Madam or Sir:

Per SUPAC Guidance "Stand Alone Packaging Operations Site Change" section of the Letter to Industry from CDER dated February 18, 1997, Mallinckrodt Inc. has concurrently submitted a Special Supplement-Changes Being Effectuated-30 Days for ANDA #89-160 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 mg/650 mg. The currently approved application provides for _____ This supplemental application provides for the addition of _____ as _____ . Mallinckrodt intends to proceed with distribution of the _____ packaged product from _____ within 30 days of the date of this submission (December 30, 2001) unless otherwise directed by FDA.

_____ has provided written certification stating that it is in conformance with cGMPs. The last FDA compliance inspection conducted at _____ occurred October 14, 1999 through November 30, 1999. The same container/closure system as described in the currently approved application will be utilized by _____ and _____ for all _____ packaging. The _____ packaging equipment at _____ operates on similar principles as the equipment in the currently approved application for use at the Mallinckrodt Hobart facility.

Mallinckrodt has also provided certification that the first production lot of the _____ product packaged at _____ will be placed on long-term stability according to the stability protocol in the currently approved application. Stability data will be provided, as it becomes available, in Annual Reports for this product.

The archival copy of this supplemental application consists of one (1) volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this ANDA, true copies of the technical sections of the ANDA were sent to the District Offices in Buffalo, NY and Cincinnati, OH. These "field copies" are contained in a maroon folder. For more detailed information on the organization of this application, please refer to "Executive Summary" which is included immediately following the Table of Contents.

Correspondence related to this submission should be addressed to Melissa Cay, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-3514 or call James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,



Melissa Cay
Senior Regulatory Affairs Associate
FAX: 314-654-6496

**APPEARS THIS WAY
ON ORIGINAL**

ANDA 40-084/S-017, S-018

APR -2 2002

Mallinckrodt Inc.
Attention: Melissa Cay
675 McDonnell Blvd.
P.O. 5840
St. Louis, MO 63134-0840

Dear Madam:

This is in reference to your supplemental new drug applications dated January 11, 2002, submitted under 505(j) of Federal Food, Drug and Cosmetic Act, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 10 mg/650 mg and 10 mg/660 mg.

These supplemental applications, submitted as "Changes Being Effected in 30 days", provide for the following changes:

S-017: The addition of 30, 60, 90 and 120 count bottle sizes

S-018: New container labels

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Labeling Deficiency:

1. CONTAINER - 30s, 60s, 90s & 120s ✓

We note that the expression of strength, 10 mg/660 mg is not sufficiently prominent due to lack of background contrast. We ask that you increase the prominence by changing the background color and/or by any other means.

**APPEARS THIS WAY
ON ORIGINAL**

2. INSERT

a. GENERAL

Although computer generated container and carton labeling is regarded acceptable as final print, it is required that you submit insert labeling in final print, not in photocopies to be acceptable. In addition, the insert labeling should be presented in one-piece, not in two-pieces as you have submitted.

b. DESCRIPTION

We encourage that you relocate the statement "Meet USP Dissolution Test 1" to appear in this section.

c. HOW SUPPLIED

See comment under DESCRIPTION.

Please revise the labels and labeling as directed above, then prepare and submit in final print as an amendment to this supplement.

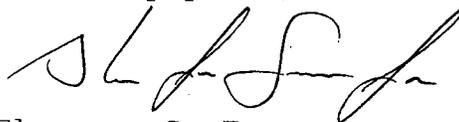
To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison with your last submission with all differences annotated and explained.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated

**APPEARS THIS WAY
ON ORIGINAL**

in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

A handwritten signature in cursive script, appearing to read 'F. S. Fang', written in black ink.

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

Mallinckrodt Inc.

675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134

Phone: (314) 654-2000
Fax: (314) 654-6496

**AMENDMENT TO A PENDING APPLICATION
MINOR AMENDMENT**

December 23, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

SUPPL AMENDMENT

SC 010
SC 011
SC 012
SC 013
SC 014
SL 015 AL

AM

**RE: ANDA 40-084: Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, 10 mg/660 mg): S-010, S-011,
S-012, S-013, S-014 and S-015**

Dear Madame or Sir:

Under 21 C.F.R. §314.120, Mallinckrodt hereby submits the following information in response to a December 17, 1999 deficiency letter from the Agency for the above referenced application.

This amendment to a pending application consists of one volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder.

This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this ANDA, true copies of the technical sections of the ANDA were sent to the local district offices. These "field copies" are contained in maroon folders. For more detailed information on the organization of this application, please refer to the "Executive Summary" which is included following the Table of Contents.

Correspondence related to this submission should be addressed to Connie McNabb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Marianne Robb at (314) 654-6258.

Sincerely,

Connie McNabb

Connie McNabb
Regulatory Affairs Associate
Phone: (314) 654-6551
Fax: (314) 654-6496



*see 21
MN*

ANDA 40-084/S-010, S-011, S-012, S-013, S-014, S-015

Mallinckrodt, Inc.
Attention: Connie McNabb
675 McDonnell Blvd.
P.O. Box 5840
St Louis, Missouri 63134

DEC 17 1999

Dear Madam:

This is in reference to your supplemental new drug applications dated June 30, 1998, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 10 mg/650 mg and 10 mg/660 mg.

Reference is also made to your amendments dated May 28, 1999 and September 2, 1999.

The supplemental applications provide for:

S-010:

[]

S-011: Formulation revision-change in components and composition.

S-012: Manufacturing revision-change from _____ to _____ and changes in manufacturing processes and procedures.

S-013: Controls revision-change in in-process specifications for major formulation and process changes.

S-014: Package revision for change in the container/closure system including HDPE bottles of 100 count, HDPE bottles of 500 count and unit dose blister packaging.

S-015: Labeling revision for new formulation.

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Regarding in-process _____ testing, it was noted that your RSD limit changes to NMT _____ if additional sample sets, beyond the initial stage are tested. We recommend a limit of _____ (mean of individual test results) with an RSD (relative standard deviation) of NMT _____ for all samples tested. Please revise.

In addition to the deficiencies presented above, please note and acknowledge the following comment in your response:

A satisfactory compliance evaluation for the facilities referenced in the supplemental application is required for approval. We have requested an evaluation from the Office of Compliance.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the supplemental applications. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a **MINOR** amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Mallinckrodt Inc.

675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134

Phone: (314) 654-2000
Fax: (314) 654-6496

AMENDMENT TO A PENDING SUPPLEMENTAL APPLICATION

NDA SUPPL AMENDMENT

September 2, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

SC-010 - Ac
SC-011 - Ac
SC-012 - Ac
SC-013 - Ac
SC-014 - Ac
SC-015 - Ac

**RE: ANDA 40-084: Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg and 10 mg/660 mg): S-010, S-011, S-012, S-013,
S-014, and S-015**

Dear Sir or Madam:

Reference is made to the above supplemental applications to ANDA 40-084 as filed on June 30, 1998 and as amended on September 29, 1998 and May 28, 1999.

The purpose of this amendment is to clarify that the specification which was previously identified as "tentative" has now been finalized. Please refer to the attached Executive Summary for a detailed discussion of these finalized specifications.

An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this amendment, true copies were sent to the local district offices. These "field copies" are contained in maroon folders.

Correspondence related to this amendment should be addressed to Connie McNabb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 654-6125.

Sincerely,

Connie McNabb

Connie McNabb
Regulatory Affairs Associate
(314) 654-6551
Fax (314) 654-6496



*Labeling review
drafted 6/9/99
A. Vezou*

Mallinckrodt Inc.

675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134

Phone: 314.654.2000
www.mallinckrodt.com

**AMENDMENT TO A PENDING APPLICATION
MAJOR AMENDMENT**

May 28, 1999

NDA SUPPL AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

*SC-010
SC-011
SC-012 AC
SC-013
SC-014
SL-015-AL*

**RE: ANDA 40-084: Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg): S-010,
S-011, S-012, S-013, S-014, S-015**

Dear Madame or Sir:

Under 21 C.F.R. §314.120, Mallinckrodt hereby submits the following information in response to an April 15, 1999 deficiency letter from the Agency for the above referenced application.

This amendment to a pending application consists of one volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. In addition, twelve copies of Final Printed Labeling are provided in a separate archival (blue) folder.

This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this ANDA, true copies of the technical sections of the ANDA were sent to the local district offices. These "field copies" are contained in maroon folders. For more detailed information on the organization of this application, please refer to the "Executive Summary" which is included immediately following the Table of Contents.

Correspondence related to this submission should be addressed to Connie McNabb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Marianne Robb at (314) 654-6258.

Sincerely,

Connie McNabb
Connie McNabb
Regulatory Affairs Associate
Phone: (314) 654-6551
Fax: (314) 654-6496



OW

ANDA 40-084/S-010, S-011, S-012, S-013, S-014, S-015

Mallinckrodt, Inc.
Attention: Connie McNabb
675 McDonnell Blvd.
P.O. Box 5840
St Louis, Missouri 63134

APR 15 1999

Dear Madam:

This is in reference to your supplemental new drug applications dated June 30, 1998 submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg

Reference is also made to your amendment dated September 30, 1998.

The supplemental applications provide for:

S-010:



S-011: Formulation revision-change in components and composition.

S-012: Manufacturing revision-change from ~~_____~~ to ~~_____~~ and changes in manufacturing processes and procedures.

S-013: Controls revision-change in in-process specifications for major formulation and process changes.

S-014: Package revision for change in the container/closure system including HDPE bottles of 100 count, HDPE bottles of 500 count and unit dose blister packaging.

S-015: Labeling revision for new formulation.

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Chemistry Deficiencies

1. There are two facilities for the manufacturing, processing, packaging and labeling, testing, stability, and release of drug product in the application. Please provide in detail the functions for each of the manufacturing sites (58 Pearl

Street and 13 Railroad Avenue).

2. The manufacturing site for _____ is located at _____ on page 3. However, the manufacturing and control site for drug substance was listed as _____ MO on page 176. Please clarify this.
3. Active ingredient _____ in a batch, for reasons of possible _____ during manufacture of the product should be examined on a case-by-case basis. Please submit the data supporting the _____ as indicated in your batch records. Please revise and resubmit.
4. Regarding _____ analysis:
 - a. The data submitted on pages 674 to 676 is not clear. Where were the samples taken from _____ and how many samples were analyzed? What is the relative standard deviation (rsd)?
 - b. Please clarify the sampling and specifications for production batches. We recommend _____ analysis acceptance criteria of _____ (mean of individual test results) with an rsd of NMT _____
5. Please include precautions concerning the control substance and the _____ of the active ingredients during manufacturing procedure on the blank batch records.
6. The proposed release specifications for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg are incomplete. Please include identification tests A & B per USP 23 Supplement 8.
7. We note that the "report on the method qualification of the _____ stability indicating method for Hydrocodone Bitartrate and Acetaminophen Tablets, USP to include alternate product formulations" was included on pages 1898-1939, however, it fails to provide an adequate stability-indicating assay method. In this regard, please provide product specific information for the following:
 - a. Brief narrative description of the procedure for _____ of the finished product under _____
 - b. List of _____ products that may be expected under _____ conditions. Establish allowable limits.

- c. Present in percentages the assay values of the active ingredients and degradation products in tabular form. Submit the chromatograms obtained for each of the conditions tested.
- d. Please specify page #s that may include the above information in your supplemental application.

Labeling Deficiencies

1. Container - 100s & 500s

- a. We encourage you to increase the prominence of "Rx only".
- b. We encourage the inclusion of the statement "Protect from light."

2. Unit dose blister

Satisfactory in draft

3. Unit dose carton - 100s

The statement "Hydrocodone Bitartrate and Acetaminophen Tablets, USP __ mg/ __ mg" on the side panel should be replaced with "Each tablet contains:..." as found on the container labels.

4. Insert labeling

a. TITLE

We encourage the inclusion of "Rx only" underneath the TITLE.

b. HOW SUPPLIED

- i. We encourage the inclusion of the statement "Protect from light."

- ii. We encourage the relocation of "Rx only" to the TITLE section.

Revise the labels and 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.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120, which will either amend or withdraw the supplemental applications. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a **MAJOR** amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

Redacted 12

Page(s) of trade

secret and /or

confidential

commercial

information

NDA SUPPL AMENDMENT

S0010, 011, 012, 013, 014

SLO15AL

AMENDMENT TO A PENDING SUPPLEMENTAL APPLICATION

September 29, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

**RE: ANDA 40-084: Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg)**

Dear Madame or Sir:

Reference is made to our supplemental application for ANDA 40-084 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/750 mg, 10 mg/650 mg, and 10 mg/660 mg) which was submitted on June 30, 1998.

The purpose of this amendment is to update documentation to reflect establishment of tablet thickness specifications. In addition, the term " _____ " was inadvertently used rather than "Silicon Dioxide NF (_____)" and the revised documentation has been included in this amendment. Furthermore, the proposed commercial batch size for the 10 mg/660 mg strength has been revised from a theoretical yield of _____ to a theoretical yield of _____ tablets. For ease of review, all changes have been highlighted.

An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. A separate copy of the bioequivalence section is being submitted in an orange folder. This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this amendment, true copies were sent to the local district offices. These "field copies" are contained in maroon folders. Two additional copies of the analytical method are contained in red folders. Four copies of the revised draft package insert are included in both the review and archival copies of the application.

RECEIVED

SEP 30 1998

GENERIC DRUGS

Correspondence related to this submission should be addressed to Connie McNabb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 654-6125.

Sincerely,

Connie McNabb

Connie McNabb
Regulatory Affairs Coordinator
(314) 654-6551
Fax (314) 654-6496

**APPEARS THIS WAY
ON ORIGINAL**



oj

*There is no
Oct 26 19*

SUPPLEMENTAL APPLICATION

November 26, 1996

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777
Telephone (314) 530-2000

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

NDA NO. _____ REF. NO. 51009
NDA SUPPL FOR Label per

*Draft approval
C. P. Talquist
1/21/97*

RE: ANDA 40-084/S-009 Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5 mg/500 mg, 7.5 mg/750 mg, 10 mg/660 mg and 10 mg/650 mg)
ANDA 89-160/S-012 Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5 mg/500 mg)
ANDA 89-725/S-015 Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5 mg/650 mg)

Gentlemen:

Mallinckrodt hereby submits a Supplemental Application for Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5 mg/500 mg, 7.5 mg/650 mg, 7.5 mg/750 mg, 10 mg/660 mg and 10 mg/650 mg) in accordance with the requirements of 21 CFR§314.70(b)(3). Specifically, this application seeks approval for a **common package insert** for both the trademarked (ANEXSIA®) product and the generic product.

King, Ph.D.

The Chemistry, Manufacturing and Controls remain as currently described in the above referenced applications.

This application consists of a single volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder.

If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. by telephone at (314) 530-2125 or via FAX at (314) 530-2496.

Sincerely,

Marianne Robb

Marianne Robb
Manager, Regulatory Submissions
(314) 530-2258

RECEIVED

NOV 2 1996

GENERIC DRUGS

*Package Insert Label
Gatis Factory - FPL
9/17/96
Albrees*

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777
Telephone (314) 530-2000

MINOR AMENDMENT

September 11, 1996

Office of Generic Drugs
Division of Chemistry II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 250
Rockville, MD 20855

NDA SUPPL AMENDMENT

*SCA 07
SL 08 /m*

RECEIVED

SEP 13 1996

GENERIC DRUGS

RE: ANDA 40-084 / S-007, S-008 Hydrocodone Bitartrate and Acetaminophen
Tablets, USP 10 mg/ 650 mg

Gentlemen:

Please find enclosed revised final printed labeling in response to an August 26, 1996 telephone conversation between Charles Hoppes of the Office of Generic Drugs and Connie McNabb of Mallinckrodt Chemical, Inc.

If there are any questions concerning this information, please contact myself or Marianne Robb at (314) 530-2258.

Sincerely,

Charles H. Smith

Charles H. Smith
Responsible Agent

MINOR AMENDMENT

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777
Telephone (314) 530-2000

August 22, 1996

Office of Generic Drugs
Division of Chemistry II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 250
Rockville, MD 20855

RECEIVED
AUG 27 1996
GENERIC DRUGS

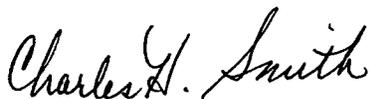
RE: ANDA 40-084 / S-007, S-008 Hydrocodone Bitartrate and Acetaminophen
Tablets, USP 10 mg/ 650 mg

Gentlemen:

Additional copies of the August 1, 1996 Minor Amendment for the above referenced file is being provided in response to an August 22, 1996 telephone conversation between Ubrani Venkataram of Office of Generic Drugs and Connie McNabb of Mallinckrodt Chemical, Inc.

If there are any questions concerning this information, please contact myself or Marianne Robb at (314) 530-2258.

Sincerely,



Charles H. Smith
Responsible Agent

cc: *Ubrani Venkataram*

MALLINCKRODT
CHEMICAL

50207, SLOS / sm
**NDA SUPPL AMENDMENT
MINOR AMENDMENT**

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777
Telephone (314) 530-2000

August 19, 1996

Office of Generic Drugs
Division of Chemistry II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 250
Rockville, MD 20855

RECEIVED

AUG 26 1996

GENERIC DRUGS

RE: ANDA 40-084 / S-007, S-008 Hydrocodone Bitartrate and Acetaminophen
Tablets, USP 10 mg/ 650 mg

Gentlemen:

Additional copies of Attachments 1 and 2 of the August 1, 1996 Minor Amendment for the above referenced file is being provided in response to a August 16, 1996 telephone conversation between Ubrani Venkataram of Office of Generic Drugs and Marianne Robb of Mallinckrodt Chemical, Inc.

If there are any questions concerning this information, please contact myself or Marianne Robb at (314) 530-2258.

Sincerely,

Charles H. Smith

Charles H. Smith
Responsible Agent

cc: *Ubrani Venkataram*

Orig



SCQ07, S-08/pur
NDA SUPPL AMENDMENT

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777
Telephone (314) 530-2000

MINOR AMENDMENT

August 1, 1996

Office of Generic Drugs
Division of Chemistry II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 250
Rockville, MD 20855

RECEIVED

AUG 5 1996

GENERIC DRUGS

RE: ANDA 40-084 / S-007, S-008 Hydrocodone Bitartrate and Acetaminophen
Tablets, USP 10 mg/ 650 mg

Gentlemen:

The following information is being provided in response to a June 10, 1996 deficiency letter for the above referenced application. For ease of review the Agency's comments have been repeated.

A. Chemistry Deficiencies

1. *The manufacturing / executed batch records are not satisfactory:*

[

]

Response:

[

]

.....
within this Amendment.

*M. G. ...
8-7-96*

Redacted 2

Page(s) of trade

secret and /or

confidential

commercial

information

the 3, 6, 9, 12, 18, and 24 month stations. The designated schedule for the demonstration batch was observed. Accelerated stability studies intended to support future ANDA submissions for solid oral dosage products will include dissolution testing at the 1 and 2 month stations.

9. *We note that the bottle description for 1000's in the stability report (page 309) does not compare with that in container/closure section (page 216). Please correct and resubmit.*

Response:

The 50 oz. bottle capacity was inadvertently stated as ~~500~~ on the referenced stability data sheet. This typographical error has been corrected by strikeover, initial, and date. A copy of the corrected page is provided as Attachment 5.

B. Labeling Deficiencies

CONTAINER:

1. *Place an asterisk (superscript) after the word "BITARTRATE" in the established name and immediately before the "(Warning...)" statement. [i.e. *(Warning: ...)]*

Response:

Copies of the revised Final Printed Labeling are provided as Attachment 6.

2. *We note that you have not indicated in your submission that the closure system for the 3s container size is CRC. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use). Your proposed container of 3 appears to be in this category. We believe that this package must comply with the Act. Please comment.*

Response:

~~_____~~ of the cap for the 3 count container listed in the ANDA, can supply a CRC closure that is fabricated from the same materials of construction, i.e. ~~_____~~, etc., as the closure originally listed. Drug product intended for distribution as samples in the 3 count container/closure system will be packaged with the CRC cap. Specifications for this cap are provided for review as Attachment 7.

UNIT DOSE BLISTER:

1. *Relocate the asterisk in the "Warning: . . ." statement to appear immediately before the parenthesis. See comment 1, above.*
2. *"Tablet" rather than "Tablets".*

UNIT DOSE CARTON: 100s (4 X 25s)

See comment 1. Under CONTAINER.

Response:

Not Applicable. The blister package has been withdrawn from the application, hence no labeling for the unit dose presentation is included within this Amendment. The unit dose package has been removed from the "How Supplied" section of the package insert.

INSERT:

1. *TITLE*

Place an asterisk (superscript) after the word "BITARTRATE" in the established name.

2. *DESCRIPTION*

- a. *Place an asterisk in the "Warning: . . ." statement immediately before the parenthesis.*
- b. *Revise the molecular weight of acetaminophen to read 151.17 as per USP 23.*

3. *HOW SUPPLIED*

Revise to read:

. . . capsule shaped tablet, scored . . .

Response:

Copies of the revised Final Printed Labeling are provided as Attachment 8.

If there are any questions concerning this information, please contact myself or Marianne Robb at (314) 530-2258.

Sincerely,

Marianne Robb for Charles Smith

Charles H. Smith
Responsible Agent

APPEARS THIS WAY
ON ORIGINAL

AND 40-084/S-007, S-008

Mallinckrodt Chemical, Inc.
Attention: Charles H. Smith
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

JUN 10 1996

Dear Sir:

This is in reference to your supplemental new drug applications dated December 8, 1995, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg.

Reference is also made to your amendments dated March 25, 1996.

The supplemental applications provide for:

- S-007: An additional product strength of Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/650 mg.
- S-008: Labeling Revision incorporating additional product strength.

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. The manufacturing/executed batch records are not satisfactory:
 - a. The packaging does not identify the packaging components in the batch record.
 - b. No in-process tests, such as an in-process are performed to assure
2. Please submit acceptance certificates for the bottles, caps and
3. Please submit specific information regarding bottles. Submit DMF references and Letter Of Authorization.

4. Does _____ test the drug product when they receive it from King/Mallinckrodt? Please note that at least an ID test is required. Please comment.
5. Does King/Mallinckrodt test the blisters received from _____ Please note that at least an ID test is required. Please comment.
6. DMF _____ is a Type I DMF and was not reviewed. We request that you submit product specific information pertaining to _____ to the ANDA. These should include DMF references and letters of authorization from component manufacturers and testing per USP 23 to qualify the components.
7. The limits for _____ (NMT _____) in the stability data sheet should be included in the stability protocol. Please revise and resubmit.
8. Dissolution data is missing for several time points in the stability report. Please explain. We recommend that you follow your stability protocol diligently.
9. We note that the bottle description for 1000's in the stability report (page 309) does not compare with that in container/closure section (page 216). Please correct and resubmit.

B. Labeling Deficiencies

CONTAINER: 3s (sample), 100s, 1000s

1. Place an asterisk (superscript) after the word "BITARTRATE" in the established name and immediately before the "(Warning...)" statement. [i.e. *(Warning:...)]
2. We note that you have not indicated in your submission that the closure system for the 3s container size is CRC. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use). Your proposed container of 3 appears to be in this category. We believe that this package must comply with the Act. Please comment.

UNIT DOSE BLISTER:

amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

MINOR AMENDMENT

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777
Telephone (314) 530-2000

May 31, 1996

Office of Generic Drugs
Division of Chemistry II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED

JUN 05 1996

GENERIC DRUGS

RE: ANDA 40-084 (S-001 & S-002), Anexsia® 10/660 (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 10 mg/660 mg)

Gentlemen:

The following information is being provided in response to an April 18, 1996 deficiency letter for the above referenced application. For ease of review the Agency's comments have been repeated.

Comment:

A. Chemistry Deficiencies

1. The _____ appears to be flawed.
Please submit a rational sampling plan taking into account _____

Response:

[]

M. Malone
1-1-96

Redacted _____

Page(s) of trade

secret and /or

confidential

commercial

information

Comment:

4. Please submit specific information regarding _____
_____ Submit DMF references and Letter of Authorization (LOA).

Response:

Attached are copies of information regarding _____

Comment:

5. Please submit DMF references and LOA from _____
for the _____

Response:

Attached is a copy of the letter for _____ which certifies
that _____ conforms to the applicable
regulations of 21 CFR 177.1520(c)1.1, 175.300 and 178.2010.

Comment:

B. Labeling Deficiencies

1. CONTAINER: 100s and 1000s
 - a. Delete the asterisk after the word "Bitartrate" in the "Each Tablet Contains:" statement and relocate it to after the word "BITARTRATE" in the established name.
 - b. Relocate the asterisk from before the word "WARNING" and relocate it to before the parenthesis - not as a superscript (i.e. * (WARNING ...)).
2. INSERT:
 - a. GENERAL COMMENT
The requirements of 21 CFR 201.10 (g)(1) must be met. The established name is to appear at least once in each column in association with the proprietary name.
 - b. DESCRIPTION
 - I. Place an asterisk immediately before the statement "(Warning...)" [see 1.b.].
 - ii. Revise the molecular weight of acetaminophen to read 151.17 as per USP 23.
 - c. OVERDOSAGE
Treatment - Fourth paragraph, first sentence. ...opioid overdose. (spelling)

Response:

Twelve copies of final printed labeling are provided. Labeling changes have been incorporated which were requested in the April 18, 1996 letter. In addition, labeling has been amended to reflect the change in ownership of the application from King Pharmaceuticals, Inc. to Mallinckrodt Chemical, Inc. and the resulting change in the NDC number, the corporate logo and the address.

If there are any questions concerning this information, please contact myself or Marianne Robb at (314) 530-2258.

Sincerely,



Charles H. Smith
Responsible Agent

CHS:cmm

APPEARS THIS WAY
ON ORIGINAL



NDA SUPPL AMENDMENT
SC-003, SL-004, SL-005, SL-006/AM

May 29, 1996

Mallinckrodt Chemical, Inc.
16305 Swingley Ridge Drive
Chesterfield, Missouri 63017-1777

Telephone (314) 530-2000

Dr. Frank O. Holcombe, Jr.
Director
Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

JUN 03 1996

GENERIC DRUGS

RE: ANDA 40-084 (S-005, S-006), Hydrocodone Bitartrate and Acetaminophen Tablets, USP (5/500) and (S-003, S-004), Hydrocodone Bitartrate and Acetaminophen Tablets, USP (7.5/750)

Dear Dr. Holcombe:

We acknowledge receipt of your letter dated May 24, 1996 regarding the above referenced supplements S-003, S-004, S-005 and S-006.

Please refer to the attached copies of our telephone amendments which were forwarded to Mr. Douglas Sporn by Federal Express on April 30, 1996 and received at your office on May 1, 1996.

If you have any questions or require any additional information, please do not hesitate to contact myself at 314-530-2128 or Marianne Robb at 314-530-2258.

Sincerely,

Charles H. Smith
Responsible Agent

cc: Mr. Tim Ames

ANDA 40-084/S-003, S-004, S-005, S-006

Mallinckrodt Chemical, Inc.
Attention: Charles H. Smith
16305 Swingley Ridge Drive
Chesterfield, MO 63017-1777

MAY 24 1996

Dear Sir:

This is in reference to your supplemental new drug applications dated July 25, 1995 (S-003, S-004) and September 1, 1995 (S-005, S-006), submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg.

The supplemental applications provide for:

- S-003: Additional packaging configuration of 1000 tablets per bottle for the 7.5 mg/750 mg product.
- S-004: Labeling revision
- S-005: Additional packaging configuration of 1000 tablets per bottle for the 5 mg/500 mg product.
- S-006: Labeling revision

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

Labeling Deficiencies

Regarding S-004 and S-006: We refer you to a telephone conversation between A. Vezza of the Agency and T. Rogers and Mary Ann Robb of the firm on March 5, 1996, concerning the following labeling comments.

1. CONTAINER: 1000s
 - a. Place an asterisk after the word "BITARTRATE" in the established name.
 - b. Delete the "(Warning:...)" statement after the established name.

- c. Place an asterisk immediately before the "(Warning:...)" statement in the "Each Tablet..." statement. [i.e. *(Warning:...)]

2. INSERT

- a. GENERAL COMMENT

Place the asterisk before the parenthesis in the "Warning..." statement [*(Warning...)] throughout the insert.

- b. DESCRIPTION

Revise the molecular weight of acetaminophen to read 151.17 as per USP 23.

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

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the supplemental applications. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

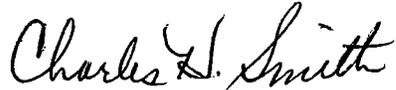
Frank O. Holcombe, Jr., Ph.D
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Douglas L. Sporn
ANDA 40-084 (S-004)

April 30, 1996
Page 2 of 2

If there are any questions concerning this application, please contact myself or Marianne Robb at (314) 530-2258.

Sincerely,



Charles H. Smith
Responsible Agent

cc: Mr. Tim Ames
Mr. Tom Rogers

APPEARS THIS WAY
ON ORIGINAL

DN

ANDA 40-084/S-001, S-002

King Pharmaceuticals, Inc.
Attention: Tom K. Rogers, III
501 Fifth Street
Bristol, TN 37620

18 MAR

Dear Sir:

This is in reference to your supplemental new drug applications dated June 30, 1995, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/500 mg and 7.5 mg/750 mg.

Reference is also made to your amendments dated November 27, 1995.

The supplemental applications provide for:

- (S-001) - An additional new product strength of Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/660 mg.
- (S-002) - Revised labels and labeling for the additional new product strength.

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. The _____ for determination of _____ Please submit a rational sampling plan taking into account _____
2. The _____ were not satisfactorily explained. It is noted that the _____ varied by a large margin between the initial test _____ and a later test (_____ Also, the _____ Was there a _____ in the _____

reading? What steps have been considered for prevention of this misstep in the future production batches?

3. The in-process sampling in support of _____ appears inadequate. Please provide a more rational sampling plan.
4. Please submit specific information regarding _____
Submit DMF references and Letter of Authorization (LOA).
5. Please submit DMF references and LOA from _____ for the _____

B. Labeling Deficiencies

1. CONTAINER: 100s and 1000s
 - a. Delete the asterisk after the word "Bitartrate" in the "Each Tablet Contains:" statement and relocate it to after the word "BITARTRATE" in the established name.
 - b. Relocate the asterisk from before the word "WARNING" and relocate it to before the parenthesis - not as a superscript (i.e. *(WARNING:...)).
2. INSERT
 - a. GENERAL COMMENT

The requirements of 21 CFR 201.10(g)(1) must be met. The established name is to appear at least once in each column in association with the proprietary name.
 - b. DESCRIPTION
 - i. Place an asterisk immediately before the statement "(Warning...)" [see 1.b.].
 - ii. Revise the molecular weight of acetaminophen to read 151.17 as per USP 23.

c. OVERDOSAGE

Treatment - Fourth paragraph, first sentence.

...opioid overdose. (spelling)

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

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

Please note that the USP methods are the official regulatory methods for this compendial product.

The file on this supplemental application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the supplemental application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a **MINOR** amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-084 /S-002

King Pharmaceuticals, Inc.
Attention: Thomas Roger, III
501 Fifth Street
Bristol TN 37620

JAN - 5 1996

Dear Sir:

This letter supersedes our previous letter dated December 13, 1995, which specified that the Division of Bioequivalence has completed their review and has no further questions. This letter corrects item number 2 of the December 13, 1995 letter, which should have stated the following:

Reference is made to your drug abbreviated new drug application dated April 27, 1993, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 660 mg/10 mg.

The following comment pertains **only** to bioequivalency issues related to your supplemental application dated in the June 20, 1995.

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

The following dissolution testing should be incorporated into your stability and quality control programs:

Dissolution testing should be conducted according to USP 23 methodology using apparatus 2 (paddle) at 50 rpm in 900 mL of pH 5.8 phosphate buffer at 37°. Each component of the test product should meet the following specification:

Not less than 80% of the labeled amount of drug to be dissolved in 30 minutes.

Please note this letter is not an approval letter for the changes proposed in the supplemental application. The bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire supplemental application, including consideration of the chemistry, manufacturing and controls, labeling or other scientific or regulatory issues.

Sincerely yours,



Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs

cc: ANDA 40-084, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File
HFD-610 J. Phillips
HFD-600 D. Hare
HFD-615 P. Rickman
HFD-650 J. Gross
HFD-600 R. West
HFD-647 U. Venkataram
HFD-613 A. Vezza
Letter Out, Bio Acceptable

Endorsements:

J. Gross

DRAFTED: JAG 12/22/95

X:\WPFILE\BIO\N40084.corr

FINALIZED: STM 01/04/96

X:\WPFILE\BIO\FINAL\N40084.corr

**APPEARS THIS WAY
ON ORIGINAL**

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620



BIOAVAILABILITY

1-800-336-7783
1-423-989-8001
Fax 1-423-989-6113

December 8, 1995

Thomas K. Rogers, III
Director, Regulatory Affairs

Charles Ganley, MD
Acting Director

NDA NO. _____ REF. NO. SCQ-007

Office of Generic Drugs, CDER, FDA

NDA SUPPL FOR New Strength

Document Control Room

NDA NO. _____ REF. NO. SL-008

Metro Park North II

7500 Standish Place, Room 1NDA SUPPL FOR Labeling Revision

Rockville, MD 20855-2773

RECEIVED

DEC 11 1995

GENERIC DRUGS

**Re: ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen Tablets, USP
SUPPLEMENT - ADDITION OF NEW STRENGTH**

Dear Dr. Ganley:

King Pharmaceuticals, Inc. is submitting herewith a Supplemental Application to its Abbreviated New Drug Application (ANDA) 40-084 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP. This application seeks approval for a **new tablet strength** containing 10 mg. hydrocodone bitartrate and 650 mg. acetaminophen.

The subject ANDA 40-084 was originally approved on June 1, 1995, for two tablet strengths, 5 mg./ 500 mg. and 7.5 mg./ 750 mg. This supplemental application for a new product strength. The reference listed drug product upon which this supplemental application is based is Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 10 mg./ 650 mg. manufactured by Mikart Laboratories (ANDA 81-223).

This application consists of one volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. A separate copy of the bioequivalence section is being submitted in an orange folder. For more detailed information on the organization of this application, please refer to the "Executive Summary" which is included immediately following the Table of Contents.

By this letter, it is further certified that a true copy of the technical sections of the application (including a copy of the 356h form and a certification that the contents are a true copy of the application filed with the Office of Generic Drugs) was sent to the Nashville District office of the FDA. This "field copy" was contained in a burgundy folder.

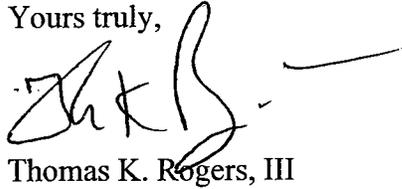
RECEIVED

DEC 11 1995

GENERIC DRUGS

Please direct any communications regarding this submission to my attention at the above address, or I may be reached by telephone at 423-989-8172 or via FAX at 423-989-6113. Thank you for your prompt attention to this application.

Yours truly,

A handwritten signature in black ink, appearing to read 'TKR', with a horizontal line extending to the right.

Thomas K. Rogers, III

cc: Mr. Tim Ames, CSO / OGD
Mr. Jefferson Gregory
Mr. John Gregory
Mr. Norman Miller

APPEARS THIS WAY
ON ORIGINAL

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620



*Labeling never done
changes needed in container label +
PI a Urgan 2/12/96*
1-800-336-7783
1-615-989-6200
Fax 1-615-989-6113

June 30, 1995

Thomas K. Rogers, III

Manager
Regulatory Affairs

Mr. Douglas L. Sporn
Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOAVAILABILITY

NDA NO. 40084 REF. NO. SC9-001

NDA SUPPL FOR Additional Strength

Re: SUPPLEMENT - ADDITION OF NEW STRENGTH

ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen Tablets, USP

Dear Mr. Sporn:

NDA NO. 40084 REF. NO. SL-002

NDA SUPPL FOR Label Revision

King Pharmaceuticals, Inc. is submitting herewith a Supplemental Application to its Abbreviated New Drug Application (ANDA) 40-084 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP. This application seeks approval for a **new tablet strength** containing 10 mg. hydrocodone bitartrate and 660 mg. acetaminophen. The company intends to market the new strength under the trade name of Anexsia® 10/660.

The subject ANDA 40-084 was originally approved on June 1, 1995, for two tablet strengths, 5 mg./ 500 mg. and 7.5 mg./ 750 mg. This supplemental application is based upon a suitability petition submitted under Docket No. 91P-0004/CP1 and approved by the Agency on October 27, 1992, as permitted under 21 USC §505(j)(2)(C) and 21 CFR 314.93. As directed in the letter approving this petition, the reference listed drug for this submission is Vicodin® ES (hydrocodone bitartrate and acetaminophen tablets, USP, 7.5 mg./ 750 mg.) manufactured by Knoll Pharmaceuticals.

In preparing this supplemental application, a question arose regarding the acceptability of submitting dual labeling (i.e., a separate insert and branded generic name) for this additional new 10/660 strength product. The Labeling Review Branch at OGD was contacted on June 5, 1995, and a full explanation of our proposal was discussed. OGD Policy and Procedure Guide No. 20-90 which requires multiple strengths of a common product to be in a single application was referenced. In addition, it was pointed out that King Pharmaceuticals already owns, manufactures and markets two other Hydrocodone Bitartrate and Acetaminophen Tablet applications (ANDA's Nos. 89-160 and 89-725) in differing strengths utilizing the proposed branded generic name "Anexsia." Unfortunately, because these two applications are much older, and based upon the restrictions in the above referenced guide, King is prohibited from supplementing those applications for its proposed product. The Chief of the Labeling Review Branch evaluated the proposal and indicated that OGD would entertain a review of the dual labeling in this case.

This application consists of two volumes. An archival copy is being filed in blue folders and a technical review copy is being filed in red folders. Two copies of the analytical methods

*11/21/95
called from
for mail
Sections III
the XIX
JW
6/20/95*

RECEIVED

JUL 03 1995

GENERIC DRUGS

validation section are provided in black folders; and a separate copy of the bioequivalence section is being submitted in an orange folder. For more detailed information on the organization of this application, please refer to the "Executive Summary" which is included immediately following the Table of Contents.

By this letter, it is further certified that a true copy of the technical sections of the application (including a copy of the 356h form and a certification that the contents are a true copy of the application filed with the Office of Generic Drugs) was sent to the Nashville District office of the FDA. This "field copy" was contained in a burgundy folder.

Please direct any communications regarding this submission to my attention at the above address, or I may be reached by telephone at 615-989-6237 or via FAX at 615-989-6113. Thank you for your prompt attention to this application.

Yours truly,

A handwritten signature in black ink, appearing to read "TRICK", with a horizontal line extending to the right from the end of the signature.

Thomas K. Rogers, II

cc: Mr. Tim Ames, CSO / OGD
Mr. Jefferson Gregory
Mr. John Gregory
Mr. Norman Miller

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620



1-800-336-7783
1-615-989-6200
Fax 1-615-989-6282

JOHN M. GREGORY
President and CEO

December 11, 1995

Charles J. Ganley, MD., Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North #2
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP.
NC

Dear Dr. Ganley,

Reference is made to our Abbreviated New Drug Applications for Anexsia® (Hydrocodone Bitartrate and Acetaminophen USP) Tablets, ANDA 89-160 for the 5.0 mg/500 mg Tablet, ANDA 89-725 for the 7.5 mg/650 mg Tablet, and to ANDA 40-084 (Hydrocodone Bitartrate and Acetaminophen USP) for the 5.0 mg/500 mg and 7.5 mg/750 mg strengths.

In accordance with 21 CFR 314.72(a)(1), we are informing you that effective December 11, 1995, ownership of these ANDA's was transferred to:

King Pharmaceuticals of Nevada, Inc.
Howard Hughes Center, Suite 200
3753 Howard Hughes Parkway
Las Vegas, Nevada 89109

King Pharmaceuticals of Nevada, Inc. was provided with a complete copy of all applications, ANDA 89-160, 89-725, and 40-084 including all supplements and records that are required to be kept under 21 CFR 314.81. A letter of acceptance of ownership from King Pharmaceuticals of Nevada, Inc. to your office is attached (with accompanying FDA forms 356h).

Outstanding regulatory issues include:

ANDA 89-160

S-011 Supplemental Application for new Regulatory Analytical method submitted on May 17, 1995.

ANDA 89-725

S-014 Supplemental Application for new Regulatory Analytical method submitted on May 17, 1995.

[REDACTED]
S-001 and

S-002 Supplemental Application for new Tablet Strength and Associated Labeling (10mg/660mg) submitted on June 30, 1995.

S-003 Supplemental Application for new package size (1000s) for 7.5/750 strength submitted on July 25, 1995.

RECEIVED

DEC 12 1995

GENERIC DRUGS

Handwritten signature and date:
12-18-95

S-004 Supplemental Application for new package size (1000's) 5/500 strength submitted on September 1, 1995.

S-005 and
S-006 Supplemental Application for new Tablet strength and Associated labeling (10mg/650mg) submitted on December 8, 1995.

All future correspondences concerning these ANDA's should be addressed to King Pharmaceuticals of Nevada, Inc.

Very truly yours,

KING PHARMACEUTICALS, INC.

A handwritten signature in black ink, appearing to read "John M. Gregory". The signature is written in a cursive style with a large, prominent "J" and "G".

John M. Gregory
President and C.E.O.

JAAB/ssl

**APPEARS THIS WAY
ON ORIGINAL**

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620



orig

1-800-336-7783
1-423-989-8001
Fax 1-423-989-6113

Thomas K. Rogers, III
Director, Regulatory Affairs

November 27, 1995

Mr. Tim Ames
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA SUPPL AMENDMENT
SCB001/AC
SL002/AL

Re: ANDA 40-084 Hydrocodone Bitartrate and Acetaminophen Tablets, USP (S-001, S-002)
Applications for Approval of a New Product Strength and Associated Labeling

Dear Mr. Ames:

The enclosed information is provided in response to your telephone request of November 27, 1995. This package contains pages 204 - 350, plus the Table of Contents, of the June 30, 1995 Supplemental Applications referenced above. The Sections contained within these pages were either missing from the original application or inadvertently mislaid prior to review by the Agency.

To assure that complete documentation is received by both the Center and the District Office, a copy of this additional information is also being forwarded to FDA's Nashville District Office.

From our conversation, it is our understanding that the review time for this application will not be adversely affected by this misplacement of documentation. We appreciate the opportunity afforded us by allowing us to supply these documents to the Agency in a timely manner. Should you have further questions, please contact me directly at 423-989-8172 or by FAX at 423-989-6113.

Sincerely,

Thomas K. Rogers, III

enclosures

cc: Mr. John Gregory
Mr. Jeff Gregory
Mr. Norman Miller
Mr. Raymond K. Hedblad, FDA - District Director

TR/40084-27.doc

RECEIVED

NOV 28 1995

GENERIC DRUGS

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620



BIOAVAILABILITY

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6113

September 1, 1995

Mr. Douglas L. Sporn
Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Thomas K. Rogers, III
Manager
Regulatory Affairs

*Labeling
review done
AUSO 2/15/96*

ANDA NO. _____ REF. NO. 5C005
NDA SUPPL FOR package add

ANDA NO. _____ REF. NO. 5C006
NDA SUPPL FOR Label new

Re: SUPPLEMENT - NEW PACKAGE SIZE (5 mg / 500 mg Tablets)
ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen Tablets, USP.

Dear Mr. Sporn:

King Pharmaceuticals, Inc. is submitting herewith a Supplemental Application to its Abbreviated New Drug Application (ANDA) 40-084 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP, in accordance with the requirements of 21 CFR 314.70(b)(2)(vii). Specifically, this application seeks approval for a new package size.

The subject ANDA 40-084 was approved on June 1, 1995, for two tablet strengths, 5 mg./ 500 mg. and 7.5 mg./ 750 mg., each strength being in packages of 100 tablets per bottle. This supplemental application contains information to support the approval of a 1000 count package for the 5 mg./ 500 mg. strength product. The application contains three month's accelerated stability data in the proposed container/closure system, drawings and specifications for the packaging components, USP testing data for the package, and proposed revisions to product labeling associated with the larger package.

I also bring to your attention the fact that the approved formulation for this tablet strength contains _____ however, the stability data within this application were generated from white tablets (i.e. tablets without _____). Subsequent to gaining approval to market the product, the firm elected to eliminate the _____ from the product formulation as permitted by 21 CFR 314.70(d)(4). This change will be reflected within the next annual report. To assure equivalence, data from a comparative dissolution study between _____ tablets and white tablets are included to demonstrate that the product is unaffected by the elimination of _____ from the formulation. No lots of _____ tablets of the 5 mg./ 500 mg. strength will be produced for commercial purposes.

This application consists of a single volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. By this letter, it is further certified that a true copy of this supplemental application (including a copy of the 356h form and a certification that the contents are a true copy of the application filed with the Office of Generic Drugs) was sent to the Nashville District office of the FDA. This "field copy" was contained in a burgundy folder.

Please direct any communications regarding this submission to my attention at the above address, or I may be reached by telephone at 615-989-8172 or via FAX at 615-989-6113. Thank you for your prompt attention to this application.

Yours truly,

Thomas K. Rogers, III
Director, Regulatory Affairs

cc: Mr. Jefferson Gregory
Mr. John Gregory
Mr. Norman Miller

RECEIVED

SEP 01 1995

GENERIC DRUGS

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620



1-800-336-7783
1-615-989-6200
Fax 1-615-989-6113

July 25, 1995

Mr. Douglas L. Sporn
Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

*Labeling
review done
2/15/96*

Thomas K. Rogers, III
Manager
Regulatory Affairs

NDA NO. 40084 REF. NO. SC003

NDA SUPPL FOR Packaging Add. DRAFT

Re: SUPPLEMENT - NEW PACKAGE SIZE (7.5 mg / 750 mg Tablets)
ANDA 40-084, Hydrocodone Bitartrate and Acetaminophen Tablets, USP

NDA NO. 40084 REF. NO. SLO04

Dear Mr. Sporn:

NDA SUPPL FOR LABELING ELL

King Pharmaceuticals, Inc. is submitting herewith a Supplemental Application to its Abbreviated New Drug Application (ANDA) 40-084 for Hydrocodone Bitartrate and Acetaminophen Tablets, USP, in accordance with the requirements of 21 CFR 314.70(b)(2)(vii). Specifically, this application seeks approval for a new package size.

The subject ANDA 40-084 was approved on June 1, 1995, for two tablet strengths, 5 mg./ 500 mg. and 7.5 mg./ 750 mg., each strength being in packages of 100 tablets per bottle. This supplemental application contains information to support the approval of a 1000 count package for the 7.5 mg./ 750 mg. strength product. The application contains three month's accelerated stability data in the proposed container/closure system, drawings and specifications for the packaging components, USP testing data for the package, and proposed revisions to product labeling associated with the larger package.

I also bring to your attention the fact that the approved formulation for this tablet strength contains _____ however, the stability data within this application were generated from white tablets (i.e. tablets without _____). Subsequent to gaining approval to market the product, the firm has elected to eliminate the _____ from the product formulation as permitted by 21 CFR 314.70(d)(4). This change will be reflected within the next annual report. To assure equivalence, data from a comparative dissolution study between _____ tablets and white tablets are included to demonstrate that the product is unaffected by the elimination of _____ from the formulation. No further lots of _____ tablets of the 7.5 mg./ 750 mg. strength will be produced for commercial purposes.

This application consists of a single volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. By this letter, it is further certified that a true copy of this supplemental application (including a copy of the 356h form and a certification that the contents are a true copy of the application filed with the Office of Generic Drugs) was sent to the Nashville District office of the FDA. This "field copy" was contained in a burgundy folder.

Please direct any communications regarding this submission to my attention at the above address, or I may be reached by telephone at 615-989-6237 (615-989-8172 after 7/30/95) or via FAX at 615-989-6113. Thank you for your prompt attention to this application.

Yours truly,

Thomas K. Rogers, III
Director, Regulatory Affairs

RECEIVED

JUL 27 1995

GENERIC DRUGS

cc: Mr. Jefferson Gregory
Mr. John Gregory
Mr. Norman Miller

95-12-8