

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

**Application Number: 20720, S01, S02, S03, S04, S05, S06,
S07**

Trade Name: REZULIN TABLETS

Generic Name: TROGLITAZONE

**Sponsor: PARKE DAVIS PHARMACEUTICAL
RESEARCH**

Approval Date(s): 4/4/97, 8/4/97, 11/19/97 and 12/15/97

Indication(s): ANTIDIABETIC AGENT

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION: 20720, S01, S02, S03, S04, S05, S06,
S07**

CONTENTS

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

CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number: 20720, S01, S02, S03, S04, S05, S06,
S07**

APPROVAL LETTER



NDA 20-720/S-001
NDA 20-720/S-004

Food and Drug Administration
Rockville MD 20857

APR 4 1997

Parke Davis Pharmaceutical Research
Attention: Mary E. Taylor, M.P.H.
Director, Worldwide Regulatory Affairs
P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Ms. Taylor:

Please refer to your supplemental new drug applications dated January 31, 1997, (Supplement-001) and February 25, 1997, (Supplement-004) received February 3 and 26, 1997, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rezulin™ (troglitazone) Tablets, 200 mg and 400 mg.

These supplemental applications provide for:

1. Supplement #001:

A. In the CLINICAL PHARMACOLOGY/Metabolism section (third paragraph):

Deletes word "nevertheless" from sentence: "The results of *in vivo* drug interaction studies tend to support this observation (see **Drug Interactions**); caution should be observed when Rezulin is used in combination with drugs known to be metabolized by one of these enzymes."

B. In the PRECAUTIONS/Drug Interactions section, adds the following new sections:

Terfenadine: Coadministration of Rezulin with terfenadine decreases plasma concentration of terfenadine and its active metabolite by 50-70% and may reduce the effectiveness of terfenadine.

Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl-estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%. These changes could result in the loss of contraception.

The above interaction with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. These findings should be considered when prescribing other CYP3A4 substrates such as cyclosporin,

tacrolimus, and some HMG-CoA reductase inhibitors.

2. Supplement #004:

A. In the CLINICAL PHARMACOLOGY/Metabolism section: rewords paragraphs #2 and #3.

B. In the PRECAUTIONS/Information for Patients section, adds the paragraphs:

Use of Rezulin can cause resumption of ovulation in women taking oral contraceptives and in patients with polycystic ovary disease. Therefore, a higher dose of an oral contraceptive or an alternative method of contraception should be considered.

Rezulin may affect other medications used in diabetic patients. Patients started on Rezulin should ask their physician to review their other medications to make sure that they are not affected by Rezulin.

C. In the PRECAUTIONS/Drug Interactions section, revises previous drug interaction section including:

- a. Changes title of "Sulfonylurea" section to "Glyburide."
- b. Adds a "Digoxin" section incorporating study results showing no Rezulin effect on the steady state pharmacokinetics of digoxin.
- c. In "Oral Contraception" section, adds wording: "Therefore, a higher dose of oral contraceptive or an alternative method of contraception should be considered."
- d. In "Terfenadine" section, changes terfenadine and active metabolite amount decreased from 30% to 50-70%.
- e. Revises last paragraph to delete Digoxin (mentioned separately now) and clarify potential for interactions with hydrochlorothiazide and sulfonylureas.

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submissions dated February 25, 1997. Accordingly, these supplemental applications are

NDA 20-720/S-001

NDA 20-720/S-004

Page 3

approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on February 25, 1997.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING for approved supplemental NDA 20-720/S-004." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Consumer Safety Officer, at (301) 443-3490.

Sincerely yours,

/s/ 4/4/97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug
Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-720/S-001
NDA 20-720/S-004
Page 4

cc:

Original NDAs 20-720
HFD-510/Div. files
HFD-510/CSO/MJohnston
HFD-510/RMisbin/AFleming/
HFD-870/HAhn/MFossler

DISTRICT OFFICE

HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.

Drafted by: Mjohnston3/31/97/March 31, 1997/File: wpfiles\n20720\S001&004
Initialed by: RMisbin3.3.97/MFossler3.4.97/HAhn3.10.97/EGalliers4.2.97
final: MJohnston4.3.97

APPROVAL (AP)

Food and Drug Administration
Rockville MD 20857NDA 20-720/S-002
NDA 20-720/S-003
NDA 20-720/S-005

AUG 4 1997

Parke Davis Pharmaceutical Research
Attention: Mary E. Taylor, M.P.H.
Director, Worldwide Regulatory Affairs
P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Ms. Taylor:

Please refer to your supplemental new drug applications dated February 3, 1997 (S-002), February 14, 1997 (S-003), and June 17, 1997 (S-005), received February 4 and 18, and June 19, 1997, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rezulin™ (troglitazone) Tablets, 200 mg and 400 mg.

We acknowledge receipt of your submissions to S-002 and S-003 dated February 14 and 20, March 14, April 3, 14, 16, and 29, May 5, 14, 16, 23, and 28, June 4, 11, and 20, and July 2 and 29, 1997. We also acknowledge the submission to S-005 dated July 8, 1997. The User Fee goal dates for these application are February 4, 1998 (S-002), February 18, 1998 (S-003), and December 19, 1997 (S-005), respectively.

These supplemental applications provide for:

1. S-002 adds the use of Rezulin™ in combination with sulfonylureas in the treatment of type II diabetes (new indication);
2. S-003 adds the use of Rezulin™ as monotherapy in type II diabetes (new indication);
3. S-005 adds a new 300 mg tablet dosage form (new strength).

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submissions dated July 8, 1997 (container labels for 300 mg tablets in bottles of 60 and 120 and blister packages) and July 29, 1997 (package insert.) Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on July 8 (300 mg container and blister labels) and July 29 (package insert), 1997.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days

NDA 20-720/S-002

NDA 20-720/S-003

NDA 20-720/S-005

Page 2

after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING for approved supplemental NDA 20-720/S-002, S-003, S-005." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you of your Phase 4 commitment

The protocol, data, and final report should be submitted to your IND for this product and a copy of each cover letter sent to this NDA. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of the commitment. The status summary should include the number of patients entered, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

NDA 20-720/S-002
NDA 20-720/S-003
NDA 20-720/S-005
Page 3

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Consumer Safety Officer, at (301) 443-3490.

Sincerely yours,

/S/ 8-4-97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug
Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Food and Drug Administration
Rockville MD 20857

NDA 20-720/S-006

Parke Davis Pharmaceutical Research
Attention: Mr. Irwin G. Martin
Vice President, FDA Liaison
Worldwide Regulatory Affairs
28000 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

NOV 19 1997

Dear Dr. Martin:

Please refer to your supplemental new drug application dated October 28, 1997, received October 29, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70(c) for Rezulin (troglitazone) Tablets. This change was to be implemented immediately.

The supplemental application provides for changes to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the prescriber package insert to reflect recent reports of hepatic dysfunction obtained from the spontaneous event reporting system.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on October 28, 1997. Accordingly, the supplemental application is approved effective on the date of this letter.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Regulatory Management Officer, at (301) 827-6423.

—
Sincerely yours,

/s/ 11-18-97

Solomon Sobel, M.D.

Director

Division of Metabolic and Endocrine Drug
Products (HFD-510)

Office of Drug Evaluation II

Center for Drug Evaluation and Research

cc: Original NDA 20-720

HFD-510/Div. files

HFD-510/MJohnston/GFleming/RMisbin/

DISTRICT OFFICE

HF-2/Medwatch (with labeling and MO Review and CSO Labeling Review)

HFD-92/DDM-DIAB (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-735/DPE (with labeling & MO Review & SCO Labeling Review) - for all NDAs
and supplements for adverse reaction changes

HFI-20/Press Office (with labeling)

Drafted by: Mjohnston/11.12.97 filename: s06aplr

Initialed by: Rmisbin11.13.97/GFleming11.13.97/Smooore11.17.97/HRhee11.13.97/

Rsteigerwalt11.17.97/EGalliers11.18.97

final: MJohnston11.18.97

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL



Food and Drug Administration
Rockville MD 20857

NDA 20-720/S-007

Parke Davis Pharmaceutical Research
Attention: Irwin G. Martin, Ph.D.
Vice President, FDA Liaison
Worldwide Regulatory Affairs
28000 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48105-1047

December 15, 1997

Dear Dr. Martin:

Please refer to your supplemental new drug application dated December 5, 1997, received December 8, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70(c) for Rezulin (troglitazone) Tablets.

We acknowledge receipt of your submission dated December 12, 1997.

The supplemental application provides for several changes to the CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the prescriber package insert to reflect changes to the monitoring for hepatic dysfunction. The supplement also creates a "Black Box" warning at the beginning of the label regarding for hepatocellular injury.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the draft labeling submitted on December 12, 1997. Accordingly, the supplemental application is approved effective on the date of this letter.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Regulatory Management Officer, at (301) 827-6423.

Sincerely yours,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug
Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA 20-720

HFD-510/Div. files

HFD-510/MJohnston/GFleming/RMisbin

DISTRICT OFFICE

HF-2/Medwatch (with labeling and MO Review and CSO Labeling Review)

HFD-92/DDM-DIAB (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-735/DPE (with labeling & CSO Labeling Review) - for all NDAs and supplements
for adverse reaction changes

HFI-20/Press Office (with labeling)

Drafted by: Mjohnston/12.10.97 filename: s07ap

Initialed by: Rmisbin12.15.97/GFleming12.30.97/Smoore12.22.97/HRhee12.22.97/

Rsteigerwalt12.30.97/EGalliers(JWeber for)12.29.97

final: Mjohnston12.15.97 (previously approved supplement on 12.15.97)

APPROVAL (AP)

APPROVAL THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER: 20720, S01, S02, S03, S04, S05,
S06, S07**

FINAL PRINTED LABELING

Labeling: _____

NDA No: _____ Re'd. _____

Reviewed by: JS 5/30/97

JUN - 2 1997

Each tablet contains
200 mg troglitazone.
Usual Dosage - See package
insert for full prescribing
information.
**Keep this and all drugs out
of the reach of children.**
Store at controlled room
temperature 20°-25°C (68°-77°F)
(See USP).
Protect from moisture.
0352G030
Exp date and lot

N 0071-0352-15

Rezulin™

(Troglitazone) Tablets

200 mg

Caution-Federal law prohibits
dispensing without prescription

30 TABLETS



 **PARKE-DAVIS**

© 1996 Warner-Lambert Co.



N 0071-0352-15 5

PARKE-DAVIS
Div of Warner-Lambert Co.
Morris Plains, NJ 07950 USA

Labeling: FA original

NDA No: 20728 Rec'd. 4-23-97

Reviewed by: _____

JUN - 2 1997

Professional Sample-
Not to be sold.
Each tablet contains
200 mg troglitazone.
Usual Dosage - See package
insert for full prescribing
information.
Keep this and all drugs out
of the reach of children.
Store at controlled room
temperature 20°-25°C (68°-77°F)
(See USP).
Protect from moisture.
0352G130
Exp date and lot

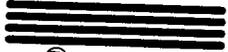
N 0071-0352-97

RezulinTM
(Troglitazone) Tablets

200 mg

Caution - Federal law prohibits
dispensing without prescription.

30 TABLETS



 **PARKE-DAVIS**

© 1996, Warner-Lambert Co.



PARKE-DAVIS
Div of Warner-Lambert Co.
Morris Plains, NJ 07950 USA

Labeling: FA original

NDA No: 20720 Rc'd. 4-23-97

Reviewed by: _____

JUN - 2 1997



Manufactured by:
PARKE-DAVIS
 Div of Warner-Lambert Co
 Morris Plains, NJ 07950 USA

Marketed by:
PARKE-DAVIS
 Div of Warner-Lambert Co and
 SANKYO/PARKE-DAVIS
 201 Tabor Road
 Morris Plains, NJ 07950
 ©1996, Warner-Lambert Co.

Each tablet contains
 200 mg of troglitazone.
Usual Dosage: See package insert for full
 prescribing information.
 Caution—Federal law prohibits dispensing without
 prescription.
 This package not child resistant.
 Keep this and all drugs out of the reach of children.
 Store at controlled room temperature 20°-25°C (68°-77°F) [See USP].
 Protect from moisture and
 humidity.
 Exp date and lot



Actual Size

PROFESSIONAL SAMPLE-NOT TO BE SOLD

7 TABLETS

ONCE-DAILY
REZULINTM
 TROGLITAZONE
 200MG
 Tablets

N 0071-0352-95

Labeling: FA Original

NDA No: 20720 Re'd. 4-23-97

Reviewed by: /S/v 5-30-97

JUN - 2 1997

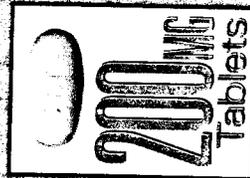
0352C060

Sample Contains 7 Days of Therapy

REZULIN™ TROGLITAZONE
200 MG TABLETS

ONCE-DAILY
REZULIN™
TROGLITAZONE
200 MG TABLETS

Sample Contains 7 Days of Therapy



REZULIN™ TROGLITAZONE
200 MG TABLETS

REZULIN™ TROGLITAZONE
200 MG TABLETS



Labeling: FA Original
NDA No: 20720 Re'd. 4-23-97
Reviewed by: 5-30-97
1/S/
JUN - 2 1997



LOT No.
EXP DATE

Sample Contains 7 Days of Therapy

N 0071-0352-95

ONCE-DAILY
REZULINTM
TROGLITAZONE
200MG
Tablets

PROFESSIONAL SAMPLE-NOT TO BE SOLD



Each tablet contains 200 mg of troglitazone.
Usual Dosage: See package insert for full prescribing information.

Caution-Federal law prohibits dispensing without prescription.

This package not child resistant.

Keep this and all drugs out of the reach of children.

Store at controlled room temperature

20°-25°C (68°-77°F) [See USP].

Protect from moisture and humidity.

See end panel for expiration date and lot number.

Manufactured by:
PARKE-DAVIS

Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

Marketed by:

PARKE-DAVIS

Div of Warner-Lambert Co and

SANKYO/PARKE-DAVIS

201 Tabor Road
Morris Plains, NJ 07950

©1996, Warner-Lambert Co.

Actual Size



0071-0352-95

REZULINTM TROGLITAZONE
200 MG TABLETS

Labeling: FA original

NDA No: 20222 Rec'd. 4-23-97

Reviewed by: JS
JUN - 2 1997

200
mg
Tablets

REZULIN
TROGLITAZONE

PARKE-DAVIS

4 PROFESSIONAL SAMPLES
(7 tablets each)

REZULIN
TROGLITAZONE
200 MG TABLETS

PARKE-DAVIS

Manufactured by
PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA
Marketed by:
PARKE-DAVIS
Div of Warner-Lambert Co and
SANKYO/PARKE-DAVIS
201 Tabor Road
Morris Plains, NJ 07950
© 1996, Warner-Lambert Co.

Exp date and lot



N 0071-0352-95



PROFESSIONAL SAMPLE-NOT TO BE SOLD

N 0071-0352-95

PROFESSIONAL SAMPLE-NOT TO BE SOLD

PARKE-DAVIS

ONCE-DAILY
REZULINTM
TROGLITAZONE
200MG
Tablets

Each tablet contains 200 mg of troglitazone.

Usual Dosage: See package insert for full prescribing information.

Caution—Federal law prohibits dispensing without prescription.

This package not child resistant.

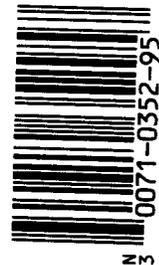
Keep this and all drugs out of the reach of children.

Store at controlled room temperature 20°-25°C (68°-77°F) [See USP].

Protect from moisture and humidity.



Actual Size



Exp date and lot

Manufactured by:
PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

Marketed by:
PARKE-DAVIS
Div of Warner-Lambert Co and
SANKYO/PARKE-DAVIS
201 Tabor Road
Morris Plains, NJ 07950
©1996, Warner-Lambert Co.

4 PROFESSIONAL SAMPLES
(7 tablets each)

AVIS

© PARKE-DAVIS

ONCE-DAILY
REZULIN
TROGLITAZONE
200 MG TABLETS



ONCE-DAILY
REZULIN
TROGLITAZONE
200 MG TABLETS



Labeling: FA original

NDA No: 20780, Rc'd. 4-23-97

Reviewed by: 1/3/97

JUN - 2 1997

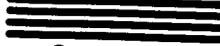
Each tablet contains
400 mg troglitazone.
Usual Dosage—See package
insert for full prescribing
information.
Keep this and all drugs out
of the reach of children.
Store at controlled room
temperature 20°-25°C (68°-77°F)
[See USP].
Protect from moisture.
0353G030
Exp date and lot

N 0071-0353-15

Rezulin™
(Troglitazone) Tablets
400 mg

Caution—Federal law prohibits
dispensing without prescription.

30 TABLETS



PARKE-DAVIS

© 1996, Warner-Lambert Co.



PARKE-DAVIS
Div of Warner-Lambert Co.
Morris Plains, NJ 07950 USA

Labeling: FA Original

NDA No: 30720 / Re'd. 4-23-97

Reviewed by: TSI / 5/30/97

JUN - 2 1997

Each tablet contains
400 mg troglitazone.

Usual Dosage—See
package insert for
full prescribing
information.

**Keep this and all
drugs out of the
reach of children.**

**Store at controlled
room temperature
20°-25°C (68°-77°F)
[See USP].**

Protect from moisture.

Exp date and lot

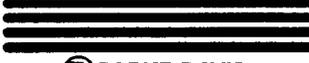
N 0071-0353-23

Rezulin™
(Troglitazone) Tablets

400 mg

Caution—Federal law prohibits
dispensing without prescription.

90 TABLETS



 **PARKE-DAVIS**



0353G050

© 1996, Warner-Lambert Co.

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

Labeling: FA 0719121
NDA No: 20709 Rc'd. 4-23-97
Reviewed by: JS 5/30/97
JUN - 2 1997

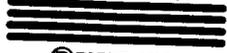
Professional Sample -
Not to be sold.
Each tablet contains
400 mg troglitazone.
Usual Dosage - See package
insert for full prescribing
information.
Keep this and all drugs out
of the reach of children.
Store at controlled room
temperature 20°-25°C (68°-77°F)
[See USP].
Protect from moisture.
0963G110
Exp date and lot

N 0071-0353-97

Rezulin™
(Troglitazone) Tablets
400 mg

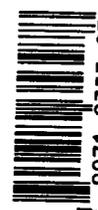
Caution - Federal law prohibits
dispensing without prescription.

30 TABLETS



PARKE-DAVIS

© 1996, Warner-Lambert Co.



N 0071-0353-97 8

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

Labeling: FA Original

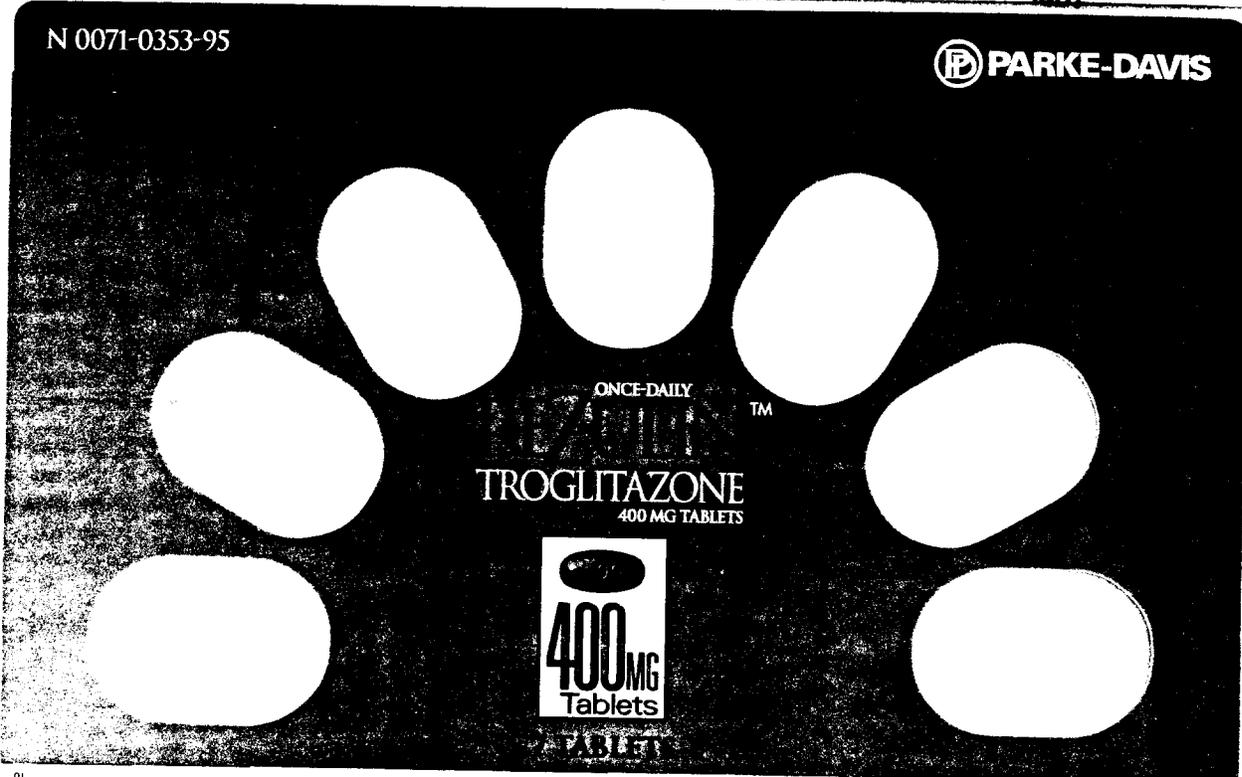
NDA No: 20720 Re'd. 4-23-97

Reviewed by: /S/ 5-30-97

JUN - 2 1997

N 0071-0353-95

PARKE-DAVIS



ONCE-DAILY

TM

TROGLITAZONE
400 MG TABLETS



400MG
Tablets



Manufactured by:
PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

Marketed by:
PARKE-DAVIS
Div of Warner-Lambert Co and
SANKYO/PARKE-DAVIS
201 Tabor Road
Morris Plains, NJ 07950
©1996, Warner-Lambert Co.

Each tablet contains
400 mg of troglitazone.
Usual Dosage: See package insert for full
prescribing information.
Caution—Federal law prohibits dispensing without
prescription.
This package not child resistant.
Keep this and all drugs out of the reach of children.
Store at controlled room temperature 20°-25°C (68°-77°F) (See USP).
Protect from moisture and
humidity.
Exp date and lot

400MG
Tablets

REZUN
ONCE-DAILY
TROGLITAZONE
TM

N 0071-0353-95

PROFESSIONAL SAMPLE-NOT TO BE SOLD

7 TABLETS

PARKE-DAVIS



Actual Size

Labeling: FA original
NDA No: 20720 Re'd. 4-23-97
Reviewed by: /S/ 5-30-97

JUN - 2 1997

0353C060

Sample Contains 7 Days of Therapy

REZULIN™ TROGLITAZONE
400 MG TABLETS

ONCE-DAILY

REZULIN™
TROGLITAZONE
400 MG TABLETS

Sample Contains 7 Days of Therapy



N 0071-0353-95

ALL PARS THIS WAY
ON ORIGINAL

REZULIN™ TROGLITAZONE
400 MG TABLETS





LOT No.
EXP DATE

N 0071-0353-95

ONCE-DAILY
REZULINTM
TROGLITAZONE
400mg
Tablets

Sample Contains 7 Days of Therapy

PROFESSIONAL SAMPLE-NOT TO BE SOLD

 **PARKE-DAVIS**

Each tablet contains 400 mg of troglitazone.
Usual Dosage: See package insert for full prescribing information.
Caution—Federal law prohibits dispensing without prescription.

This package not child resistant.

Keep this and all drugs out of the reach of children.

Store at controlled room temperature 20°-25°C (68°-77°F) [See USP].

Protect from moisture and humidity.

See end panel for expiration date and lot number.

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Actual Size



N 3

REZULINTM TROGLITAZONE
400 MG TABLETS

Sample Contains 7 Days of Therapy

Labeling: FA Original

NDA No: 20720 Re'd. 4-23-97

Reviewed by: /S/ 5-30-97

JUN - 2 1997

 PARKE-DAVIS

TROGLITAZONE
400 MG TABLETS



ONCE-DAILY

TM

 PARKE-DAVIS

ONCE-DAILY
TROGLITAZONE
400 MG TABLETS

4 PROFESSIONAL SAMPLES
(7 tablets each)

Manufactured by:
PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA
Marketed by:
PARKE-DAVIS
Div of Warner-Lambert Co and
SANKYO/PARKE-DAVIS
201 Labor Road
Morris Plains, NJ 07950
©1996, Warner-Lambert Co.

Exp date and lot



ZM

N 0071-0353-95



PROFESSIONAL SAMPLE-NOT TO BE SOLD

N 0071-0353-95

PROFESSIONAL SAMPLE-NOT TO BE SOLD

PARKE-DAVIS

ONCE-DAILY
REZULINTM
TROGLITAZONE

400MG
Tablets

Each tablet contains 400 mg of troglitazone.

Usual Dosage: See package insert for full prescribing information.

Caution-Federal law prohibits dispensing without prescription.

This package not child resistant.

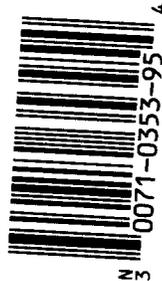
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Protect from moisture and humidity.



Actual Size



NM

Exp date and lot

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4 PROFESSIONAL SAMPLES
(7 tablets each)

© PARKE-DAVIS

ONCE-DAILY
REZULINTM
TROGLITAZONE
400 MG TABLETS



ONCE-DAILYTM

REZULINTM
TROGLITAZONE
400 MG TABLETS

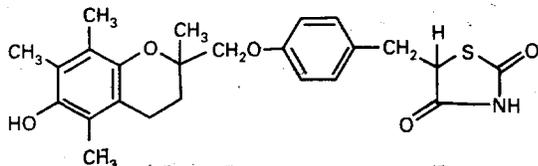


Rezulin™

(Troglitazone) Tablets

DESCRIPTION

Rezulin™ (troglitazone) is an oral antihyperglycemic agent which acts primarily by decreasing insulin resistance. Rezulin is used in the management of type II diabetes (noninsulin-dependent diabetes mellitus (NIDDM) also known as adult-onset diabetes). It improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Troglitazone (\pm 5-[[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione) is not chemically or functionally related to either the sulfonylureas, the biguanides, or the α -glucosidase inhibitors. The molecule contains 2 chiral centers, with each of the 4 stereoisomers having similar pharmacologic effects. The structural formula is as shown:



Troglitazone is a white to yellowish crystalline compound; it may have a faint, characteristic odor. Troglitazone has a molecular formula of $C_{24}H_{26}NO_5S$ and a molecular weight of 441.55 daltons. It is soluble in N,N-dimethylformamide or acetone; sparingly soluble in ethyl acetate; slightly soluble in acetonitrile, anhydrous ethanol, or ether; and practically insoluble in water.

Rezulin is available as 200 and 400 mg tablets for oral administration formulated with the following excipients: croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polysorbate 80, povidone, purified water, silicon dioxide, titanium dioxide, and synthetic iron oxides.

CLINICAL PHARMACOLOGY

Mechanism of Action

Troglitazone is a thiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin. It has a unique mechanism of action that is dependent on the presence of insulin for activity. Troglitazone decreases hepatic glucose output and increases insulin-dependent glucose disposal in skeletal muscle. Its mechanism of action is thought to involve binding to nuclear receptors (PPAR) that regulate the transcription of a number of insulin responsive genes critical for the control of glucose and lipid metabolism. Unlike sulfonylureas, troglitazone is not an insulin secretagogue.

In animal models of diabetes, troglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type II diabetes. Plasma lactate and ketone body formation are also decreased. The metabolic changes produced by troglitazone result from the increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance. Treatment with troglitazone did not affect pancreatic weight, islet number or glucagon content, but did increase regranulation of the pancreatic beta cells in rodent models of insulin resistance.

Since troglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Maximum plasma concentration (C_{max}) and the area under plasma concentration-time curve (AUC) of troglitazone increase proportionally with increasing doses over the dose range of 200 to 600 mg/day (Table 1). Following daily drug administration, steady-state plasma concentrations of troglitazone are reached within 3 to 5 days.

TABLE 1. Mean (\pm SD) Steady-State Pharmacokinetics of Troglitazone in 21 Normal Volunteers

Dose (mg/day)	C_{max} (μ g/mL)	AUC (0-24) (μ g-hr/mL)	CL/F* (mL/min)
200	0.90 (0.36)	7.4 (2.4)	500 (187)
400	1.61 (0.69)	13.4 (5.5)	601 (324)
600	2.82 (1.03)	22.1 (6.8)	496 (166)

*CL/F = Apparent oral clearance.

Absorption: Troglitazone is absorbed rapidly following oral administration; the time for maximum plasma concentration (t_{max}) occurs within 2 to 3 hours. Food increases the extent of absorption by 30% to 85%; thus Rezulin should be taken with a meal to enhance systemic drug availability.

Distribution: Mean apparent volume of distribution (V/F) of troglitazone following multiple-dose administration ranges from 10.5 to 26.5 L/kg of body weight. Troglitazone is extensively bound (>99%) to serum albumin. [14 C]troglitazone partitions into red blood cells (~5% of whole blood radioactivity).

Metabolism: In 6 healthy male volunteers given a single 400 mg dose of [14 C]troglitazone after 14 days of treatment with 400 mg troglitazone tablets, the major metabolites found in the plasma were the sulfate conjugate (Metabolite 1), followed by the quinone metabolite (Metabolite 3). Only 3.1% of the dose was detected in the urine; this was primarily in the form of the glucuronide conjugate (Metabolite 2), which is present in negligible amounts in the plasma. In both normal volunteers and patients with type II diabetes, steady-state levels of Metabolite 1 are 6 to 7 times that of troglitazone and Metabolite 3.

Troglitazone incubated with expressed human P450 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, and 3A4 in the presence and absence of known inhibitors of these enzymes showed no Metabolite 3 formation above levels in control samples. Incubation of Metabolite 3 with human liver microsomes suggests that it is not subject to further metabolism.

Rezulin™ (Troglitazone) Tablets

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that Rezulin improves insulin sensitivity in insulin-resistant patients. Rezulin increases insulin-dependent glucose disposal, reduces hepatic gluconeogenesis, and enhances cellular responsiveness to insulin and thus, improves dysfunctional glucose homeostasis. In patients with type II diabetes, the decreased insulin resistance produced by Rezulin causes decreases in serum glucose, plasma insulin, and hemoglobin A_{1c}. These effects are independent of weight loss and persist with Rezulin treatment.

Following Rezulin treatment, LDL, HDL, and total cholesterol (total-C) increase, although total-C/HDL and LDL/HDL ratios do not change. The increase in total cholesterol is due to the increase in HDL and LDL cholesterol. Despite the observed increase in total and LDL cholesterol, ApoB fraction levels are not increased. Patients treated with Rezulin and concomitant insulin exhibit an initial reduction in triglyceride levels. With the reduction in insulin doses that may occur following Rezulin therapy, some attenuation of the triglyceride reduction may occur.

Pharmacokinetic estimators of systemic troglitazone exposure do not improve the prediction of pharmacodynamic response beyond that obtained based upon knowledge of the administered dose.

Rezulin has only been shown to exert its antihyperglycemic effect in the presence of insulin. Because Rezulin does not stimulate insulin secretion, hypoglycemia in patients treated with Rezulin alone is not to be expected. Because of this insulin-dependent mechanism of action, Rezulin should not be used in patients with type II diabetes.

Clinical Studies

Two clinical studies were conducted to evaluate the effects of Rezulin on glycemic control and insulin dose in patients with type II diabetes who were being treated with insulin.

In one 6-month, double-blind, placebo-controlled study in insulin-treated type II diabetic patients receiving a mean of 73 (range 27-143) units/day of insulin with a mean baseline HbA_{1c} of 9.42 (range 7.04-12.48), Rezulin (200 or 600 mg/day) or placebo was added to the insulin therapy. Investigators were instructed to reduce insulin doses only if two consecutive FSGs were \leq 100 mg/dL. Rezulin-treated patients showed a significant ($p < 0.0001$) reduction in HbA_{1c} compared with patients who received placebo (see Table 2).

Thirty percent of patients treated with 200 mg Rezulin and 57% of patients treated with 600 mg Rezulin had an HbA_{1c} value below 8% at the end of the study compared with 11% of placebo-treated patients. Accompanying this improvement in glycemic control was a significant ($p < 0.0001$) decrease in exogenous insulin dosage of 15% in the 200 mg Rezulin treatment group and 42% in the 600 mg Rezulin treatment group compared with 1% in the placebo group. HbA_{1c} values and insulin dose as a function of duration of Rezulin treatment are presented in Figures 1 and 2.

TABLE 2. Mean Change From Baseline at 6 Months

Parameter	Placebo	Troglitazone	
		200 mg	600 mg
N	118	116	116
HbA _{1c} , %			
Mean Baseline (SE)	9.43 (0.10)	9.51 (0.10)	9.32 (0.11)
Mean Change From Baseline (SE) ¹	-0.12 (0.10)	-0.84 (0.10)	-1.41 (0.10)
Adjusted Mean Difference From Placebo (SE)	--	-0.72 (0.14)*	-1.29 (0.14)*
Percent Mean Change From Baseline	-1.3	-8.8	-15.1
Insulin daily dosage, units			
Mean Baseline (SE)	75 (3.3)	73 (3.4)	71 (2.9)
Mean Change From Baseline (SE)	1 (2.1)	-11 (2.1)	-29 (2.2)
Adjusted Mean Difference From Placebo (SE)	--	-12 (3.0)*	-30 (3.0)*
Percent Mean Change From Baseline	1	-15	-42

* $p \leq 0.0001$

¹Least squares mean adjusted for investigator center and baseline

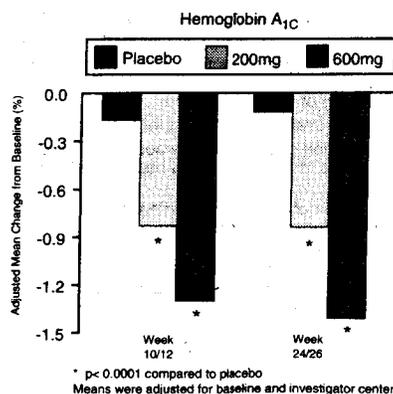
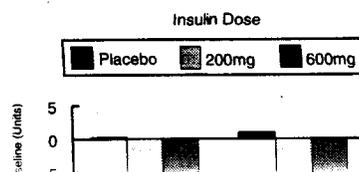


FIGURE 1



resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Maximum plasma concentration (C_{max}) and the area under plasma concentration-time curve (AUC) of troglitazone increase proportionally with increasing doses over the dose range of 200 to 600 mg/day (Table 1). Following daily drug administration, steady-state plasma concentrations of troglitazone are reached within 3 to 5 days.

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600	2.82 (1.03)	22.1 (6.8)	496 (166)

*CL/F = Apparent oral clearance.

Absorption: Troglitazone is absorbed rapidly following oral administration; the time for maximum plasma concentration (t_{max}) occurs within 2 to 3 hours. Food increases the extent of absorption by 30% to 85%; thus Rezulin should be taken with a meal to enhance systemic drug availability.

Distribution: Mean apparent volume of distribution (V/F) of troglitazone following multiple-dose administration ranges from 10.5 to 26.5 L/kg of body weight. Troglitazone is extensively bound (>99%) to serum albumin. [¹⁴C]troglitazone partitions into red blood cells (~5% of whole blood radioactivity).

Metabolism: In 6 healthy male volunteers given a single 400 mg dose of [¹⁴C]troglitazone after 14 days of treatment with 400 mg troglitazone tablets, the major metabolites found in the plasma were the sulfate conjugate (Metabolite 1), followed by the quinone metabolite (Metabolite 3). Only 3.1% of the dose was detected in the urine; this was primarily in the form of the glucuronide conjugate (Metabolite 2), which is present in negligible amounts in the plasma. In both normal volunteers and patients with type II diabetes, steady-state levels of Metabolite 1 are 6 to 7 times that of troglitazone and Metabolite 3.

Troglitazone incubated with expressed human P450 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, and 3A4 in the presence and absence of known inhibitors of these enzymes showed no Metabolite 3 formation above levels in control samples. Incubation of Metabolite 3 with human liver microsomes suggests that it is not subject to further metabolism.

The inhibitory profile of troglitazone against the 7 major P450 isozymes was characterized using human liver microsomes. Troglitazone was found to inhibit 3A4, 2C9, and 2C19 by 40% to 67% at a concentration of 11 µg/mL. Since the highest peak concentrations expected to be achieved on 600 mg once daily is in the range of 1 to 3 µg/mL, inhibition may not be clinically important. The results of *in vivo* drug interaction studies tend to support this observation (see Drug Interactions); caution should be observed when Rezulin is used in combination with drugs known to be metabolized by one of these enzymes. The inhibitory characteristics of Metabolite 3 have not been investigated directly.

Excretion: Following oral administration of [¹⁴C]troglitazone, approximately 88% of the radioactivity is recovered in feces (85%) and urine (3%). Unchanged troglitazone is not recovered in urine following oral administration. Mean plasma elimination half-life of troglitazone ranges from 16 to 34 hours.

Special Populations

Renal Insufficiency: In patients with various degrees of renal function, the apparent clearance of total and unbound troglitazone and the plasma elimination half-life of troglitazone, Metabolite 1, and Metabolite 3 do not correlate with creatinine clearance. Thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Troglitazone, Metabolite 1, and Metabolite 3 plasma concentrations in patients with chronic liver disease (Childs-Pugh Grade B or C) were increased by approximately 30%, 400% and 100%, respectively, compared to those in healthy subjects without hepatic dysfunction. There was no change in plasma protein binding. No adverse events were noted in any group that were attributed to drug. Nevertheless, Rezulin should be used with caution in patients with hepatic disease.

Geriatrics: Steady-state pharmacokinetics of troglitazone, Metabolite 1, and Metabolite 3 in healthy elderly subjects are comparable to those seen in young adults.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of troglitazone and its metabolites are similar in men and women.

Ethnicity: Pharmacokinetics of troglitazone and its metabolites are similar among various ethnic groups.

Mean Baseline (SE)	75 (3.3)	73 (3.4)	71 (2.9)
Mean Change From Baseline (SE)	1 (2.1)	-11 (2.1)	-29 (2.2)
Adjusted Mean Difference From Placebo (SE)	-	-12 (3.0)*	-30 (3.0)*
Percent Mean Change From Baseline	1	-15	-42

* p ≤ 0.0001

[†]Least squares mean adjusted for investigator center and baseline

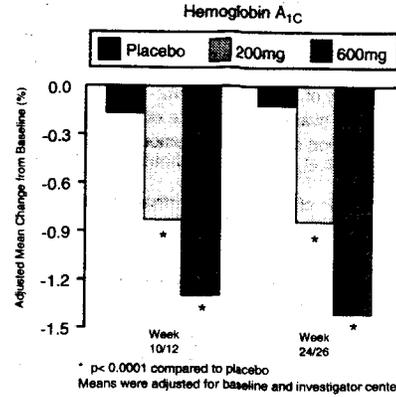


FIGURE 1

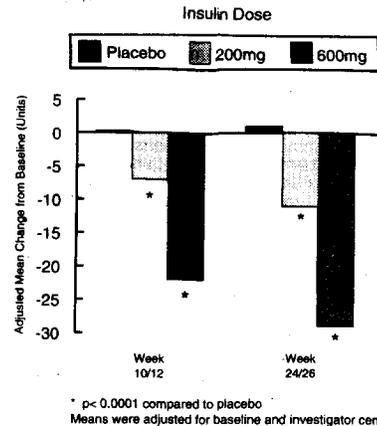
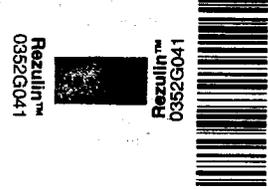


FIGURE 2

A second 6-month, double-blind, placebo-controlled study in insulin-treated type II diabetics who previously were poorly controlled on oral agents receiving 30 to 150 units insulin/day assessed the use of Rezulin in reducing exogenous insulin dosage while improving glycemic control as measured by capillary blood glucose. Patients treated with 200 mg (N=75) and 400 mg (N=76) Rezulin had their insulin doses decreased by 41% and 58%, respectively, compared to a reduction of insulin dose in the placebo group (N=71) of 14% while maintaining or improving glycemic control. Forty-one percent of the patients in the 400 mg group decreased their insulin injection frequency an average from 3 to 1 injections per day; 19% of patients receiving placebo decreased their injection frequency an average from 3 to 2 injections per day. Insulin therapy was discontinued in 15% of patients in the 400 mg Rezulin group compared to 7% in the 200 mg group and 1.5% in the placebo group.

PARKE-DAVIS



Rezulin™ (Troglitazone) Tablets

A greater than 50% reduction in insulin dose was achieved by 51% of patients on 200 mg and 70% on 400 mg once daily as compared to 17% on placebo.

An extended open-label study of Rezulin (N=17), has followed insulin-treated type II diabetic patients for up to 9 months. Following 9 months of treatment with 400 mg of Rezulin, mean HbA_{1c} levels were decreased by 0.8% compared with baseline values of 11.8% ± 2.0% (mean ± SD). The mean insulin daily dose decreased by 71% (42 units/day) in these seventeen patients.

INDICATIONS AND USAGE

Rezulin is indicated for use in patients with type II diabetes currently on insulin therapy whose hyperglycemia is inadequately controlled (HbA_{1c} >8.5%) despite insulin therapy of over 30 units per day given as multiple injections.

Management of type II diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only in the primary treatment of type II diabetes, but in maintaining the efficacy of drug therapy. Prior to initiation of Rezulin therapy, secondary causes of poor glycemic control, eg, infection or poor injection technique, should be investigated and treated.

CONTRAINDICATIONS

Rezulin is contraindicated in patients with known hypersensitivity or allergy to Rezulin or any of its components.

PRECAUTIONS

General

Because of its mechanism of action, Rezulin is active only in the presence of insulin. Therefore, Rezulin should not be used in type I diabetes or for the treatment of diabetic keto-acidosis.

Hepatic: During all clinical studies in North America (N=2510 patients), a total of 20 Rezulin-treated patients were withdrawn from treatment because of liver function test abnormalities. Two of the 20 patients developed reversible jaundice. Both had liver biopsies which were consistent with an idiosyncratic drug reaction (see ADVERSE REACTIONS, Laboratory Abnormalities).

Hypoglycemia: Patients receiving Rezulin in combination with insulin may be at risk for hypoglycemia and a reduction in the dose of insulin may be necessary. Hypoglycemia has not been observed during the administration of Rezulin as monotherapy and would not be expected based on the mechanism of action.

Ovulation: In premenopausal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. **These patients may be at risk for pregnancy.**

Hematologic: Across all clinical studies, hemoglobin declined by 3 to 4% in troglitazone-treated patients compared with 1 to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazone-treated patients compared to those treated with placebo. These changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy. These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects (See ADVERSE REACTIONS, Laboratory Abnormalities).

Information for Patients

Rezulin should be taken with meals. If the dose is missed at the usual meal, it may be taken at the next meal. If the dose is missed on one day, the dose should not be doubled the following day.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. During periods of stress such as fever, trauma, infection, or surgery, insulin requirements may change and patients should seek the advice of their physician.

When using combination therapy with insulin, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Drug Interactions

Cholestyramine: Concomitant administration of cholestyramine with Rezulin reduces the absorption of troglitazone by approximately 70%; thus, coadministration of cholestyramine and Rezulin is not recommended.

Acetaminophen: Coadministration of acetaminophen and Rezulin does not alter the pharmacokinetics of either drug.

Warfarin: Rezulin has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Sulfonylureas: Coadministration of Rezulin with glyburide does not appear to alter troglitazone or glyburide pharmacokinetics, but may further decrease fasting plasma glucose. There are insufficient data on the use of Rezulin with sulfonylureas to establish the efficacy of this combination.

Metformin: No information is available on the use of Rezulin with metformin.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Rezulin-treated patients with type II diabetes mellitus.

Terfenadine: Coadministration of Rezulin with terfenadine decreases plasma concentrations of terfenadine and its active metabolite by 50 to 70% and may reduce the effectiveness of terfenadine.

Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%. These changes could result in loss of contraception.

The above interactions with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. These findings should be considered when prescribing other CYP3A4 substrates such as cyclosporine, tacrolimus and some HMG-CoA reductase inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Troglitazone was administered daily for 104 weeks to male rats at 100, 400, or 800 mg/kg and to female rats at 25, 50, or 200 mg/kg. Maximum plasma troglitazone AUC values based on parent compound represent exposures 12- and 47-fold higher for male and female rats, respectively, than human exposure of 400 mg daily. Troglitazone was not carcinogenic in male rats at any dose tested. In female rats, there was a statistically significant increase in sarcomatous tumors at the high dose (47-fold greater than estimated human exposure at this dose was associated). These findings are of unknown clinical relevance as this dose was associated with excessive mortality and is considered to have surpassed the maximum tolerated dose. No tumors of any type were increased in female rats at 25 and 50 mg/kg. No tumors of any type were increased in male rats at 100, 400, or 800 mg/kg. No tumors of any type were increased in female rats at 25 and 50 mg/kg. No tumors of any type were increased in male rats at 100, 400, or 800 mg/kg.

Rezulin™ (Troglitazone) Tablets

Nursing Mothers

It is not known whether troglitazone is secreted in human milk. Troglitazone is secreted in the milk of lactating rats. Because many drugs are excreted in human milk, Rezulin should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Twenty-two percent of patients in clinical trials of Rezulin were 65 and over. No differences in effectiveness and safety were observed between these patients and younger patients.

Use in Patients With Heart Failure

Heart enlargement without microscopic changes has been observed in rodents at exposures exceeding 14 times the AUC of the 400 mg human dose. Serial echocardiographic evaluations in monkeys treated chronically at maximum achievable exposures (3-5 times the human exposure at the 400 mg dose) did not reveal changes in heart size or function. In a 2-year echocardiographic clinical study using 600 to 800 mg/day of Rezulin in patients with type II diabetes, no increase in left ventricular mass or decrease in cardiac output was observed. The methodology employed was able to detect a change of about 10% or more in left ventricular mass.

In animal studies, troglitazone treatment was associated with increases of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase in plasma volume of 6% to 8% compared to placebo was observed following 6 weeks of troglitazone treatment.

No increased incidence of adverse events potentially related to volume expansion (eg, congestive heart failure) have been observed during controlled clinical trials. However, patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials. Therefore, caution is advised during the administration of Rezulin to patients with NYHA Class III or IV cardiac status.

ADVERSE REACTIONS

In general, Rezulin is well-tolerated. Two patients in the clinical studies developed reversible jaundice with findings on liver biopsy consistent with idiosyncratic drug reaction (See PRECAUTIONS, General).

The overall incidence and types of adverse reactions reported in placebo-controlled clinical trials for Rezulin-treated patients and placebo-treated patients are shown in Table 3. In patients treated with Rezulin in glyburide-controlled studies (N=550) or uncontrolled studies (N=510), the safety profile of Rezulin appeared similar to that displayed in Table 3. The incidence of withdrawals during clinical trials was similar for patients treated with placebo or Rezulin (4%).

TABLE 3. North American Placebo-Controlled Clinical Studies: Adverse Events Reported at a Frequency ≥ 5% of Rezulin-Treated Patients

	Placebo N = 492	Rezulin N = 1450
Infection	22	18
Headache	11	11
Pain	14	10
Accidental Injury	6	8
Asthenia	5	6
Dizziness	5	6
Back Pain	4	6
Nausea	4	6
Rhinitis	7	5
Diarrhea	6	5
Urinary Tract Infection	6	5
Peripheral Edema	5	5
Pharyngitis	4	5

Types of adverse events seen when Rezulin was used concomitantly with insulin (N=543) were similar to those during Rezulin monotherapy (N=1731), although hypoglycemia occurred on insulin combination therapy (see PRECAUTIONS).

Laboratory Abnormalities

Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the normal range occurred in 5% of Rezulin-treated and 4% of placebo-treated patients.

Lipids: Small changes in serum lipids have been observed (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

Serum Transaminase Levels: During controlled clinical trials, 2.2% of Rezulin-treated patients had reversible elevations in AST or ALT greater than 3 times the upper limit of normal, compared with 0.6% of patients receiving placebo. Hypert bilirubinemia (>1.25 upper limit of normal) was found in 0.7% of Rezulin-treated patients compared with 1.7% of patients receiving placebo. In the population of patients treated with Rezulin, mean and median values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline, while values for LDH were increased slightly (see PRECAUTIONS, General, Hepatic).

DOSAGE AND ADMINISTRATION

The current insulin dose should be continued upon initiation of Rezulin therapy. Rezulin therapy should be initiated at 200 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Rezulin should be increased after approximately 2 to 4 weeks. The usual dose of Rezulin is 400 mg once daily. The maximum recommended daily dose is 600 mg. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and Rezulin. Further adjustments should be individualized based on glucose-lowering response. Rezulin should be taken with a meal.

Patients With Renal Insufficiency

Dose adjustment in patients with renal insufficiency is not required (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Patients With Hepatic Impairment

Dose adjustment in patients with hepatic impairment is not required (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

risk for hypoglycemia and a reduction in the dose of insulin may be necessary. Hypoglycemia has not been observed during the administration of Rezulin as monotherapy and would not be expected based on the mechanism of action.

Ovulation: In premenopausal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. **These patients may be at risk for pregnancy.**

Hematologic: Across all clinical studies, hemoglobin declined by 3 to 4% in troglitazone-treated patients compared with 1 to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazone-treated patients compared to those treated with placebo. These changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy. These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects (See ADVERSE REACTIONS, Laboratory Abnormalities).

Information for Patients

Rezulin should be taken with meals. If the dose is missed at the usual meal, it may be taken at the next meal. If the dose is missed on one day, the dose should not be doubled the following day.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. During periods of stress such as fever, trauma, infection, or surgery, insulin requirements may change and patients should seek the advice of their physician.

When using combination therapy with insulin, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Drug Interactions

Cholestyramine: Concomitant administration of cholestyramine with Rezulin reduces the absorption of troglitazone by approximately 70%; thus, coadministration of cholestyramine and Rezulin is not recommended.

Acetaminophen: Coadministration of acetaminophen and Rezulin does not alter the pharmacokinetics of either drug.

Warfarin: Rezulin has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Sulfonylureas: Coadministration of Rezulin with glyburide does not appear to alter troglitazone or glyburide pharmacokinetics, but may further decrease fasting plasma glucose. There are insufficient data on the use of Rezulin with sulfonylureas to establish the efficacy of this combination.

Metformin: No information is available on the use of Rezulin with metformin.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Rezulin-treated patients with type II diabetes mellitus.

Terfenadine: Coadministration of Rezulin with terfenadine decreases plasma concentrations of terfenadine and its active metabolite by 50 to 70% and may reduce the effectiveness of terfenadine.

Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%. These changes could result in loss of contraception.

The above interactions with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. These findings should be considered when prescribing other CYP3A4 substrates such as cyclosporine, tacrolimus and some HMG-CoA reductase inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Troglitazone was administered daily for 104 weeks to male rats at 100, 400, or 800 mg/kg and to female rats at 25, 50, or 200 mg/kg. Maximum plasma troglitazone AUC values based on parent compound represent exposures 12- and 47-fold higher for male and female rats, respectively, than human exposure of 400 mg daily. Troglitazone was not carcinogenic in male rats at any dose tested. In female rats, there was a statistically significant increase in sarcomatous tumors at the high dose (47-fold greater than estimated human exposure of parent compound). However, these findings are of unknown clinical relevance as this dose was associated with excessive mortality and is considered to have surpassed the maximum tolerated dose. No tumors of any type were increased in female rats at 25 and 50 mg/kg at exposures of 5- to 14-fold higher than in humans based on AUC of parent compound. In a 104-week study in mice given 50, 400, or 800 mg/kg, incidence of hemangiosarcoma was increased in females at 400 mg/kg and in both sexes at 800 mg/kg; incidence of hepatocellular carcinoma was increased in females at 800 mg/kg. The lowest dose with increased tumor incidence (400 mg/kg) was associated with AUC values of parent compound that were at least 16-fold higher than the human exposure. No tumors of any type were increased in mice at 50 mg/kg at exposures 2- to 4-fold higher than in humans based on AUC of parent compound.

Troglitazone was neither mutagenic in bacteria nor clastogenic in bone marrow of mice. Equivocal increases in chromosome aberrations were observed in an *in vitro* Chinese hamster lung cell assay. In mouse lymphoma cell gene mutations assays, results were equivocal when conducted with a microtiter technique and negative with an agar plate technique. A liver unscheduled DNA synthesis assay in rats was negative.

No adverse effects on fertility or reproduction were observed in male or female rats given 40, 200, or 1000 mg/kg daily prior to and throughout mating and gestation. AUC at these doses was estimated to be 2- to 8-fold higher than the human exposure.

Pregnancy

Pregnancy Category B. Troglitazone was not teratogenic in rats given up to 2000 mg/kg or rabbits given up to 1000 mg/kg during organogenesis. Compared to human exposure of 400 mg daily, estimated exposures based on AUC at these doses were up to 8-fold higher in rats and up to 6-fold higher in rabbits. Body weights of fetuses and offspring of rats given 2000 mg/kg during gestation were decreased. Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats given 40, 200, or 1000 mg/kg during late gestation and lactation periods; no effects were observed in offspring of rats given 10 or 20 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Rezulin should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

In general, Rezulin is well-tolerated. Two patients in the clinical studies developed reversible jaundice with findings on liver biopsy consistent with idiosyncratic drug reaction (See PRECAUTIONS, General).

The overall incidence and types of adverse reactions reported in placebo-controlled clinical trials for Rezulin-treated patients and placebo-treated patients are shown in Table 3. In patients treated with Rezulin in glyburide-controlled studies (N=550) or uncontrolled studies (N=510), the safety profile of Rezulin appeared similar to that displayed in Table 3. The incidence of withdrawals during clinical trials was similar for patients treated with placebo or Rezulin (4%).

TABLE 3. North American Placebo-Controlled Clinical Studies: Adverse Events Reported at a Frequency \geq 5% of Rezulin-Treated Patients

	Placebo N = 492	Rezulin N = 1450
Infection	22	18
Headache	11	11
Pain	14	10
Accidental Injury	6	8
Asthenia	5	6
Dizziness	5	6
Back Pain	4	6
Nausea	4	6
Rhinitis	7	5
Diarrhea	6	5
Urinary Tract Infection	6	5
Peripheral Edema	5	5
Pharyngitis	4	5

Types of adverse events seen when Rezulin was used concomitantly with insulin (N=543) were similar to those during Rezulin monotherapy (N=1731), although hypoglycemia occurred on insulin combination therapy (see PRECAUTIONS).

Laboratory Abnormalities

Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the normal range occurred in 5% of Rezulin-treated and 4% of placebo-treated patients.

Lipids: Small changes in serum lipids have been observed (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

Serum Transaminase Levels: During controlled clinical trials, 2.2% of Rezulin-treated patients had reversible elevations in AST or ALT greater than 3 times the upper limit of normal, compared with 0.6% of patients receiving placebo. Hyperbilirubinemia (>1.25 upper limit of normal) was found in 0.7% of Rezulin-treated patients compared with 1.7% of patients receiving placebo. In the population of patients treated with Rezulin, mean and median values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline, while values for LDH were increased slightly (see PRECAUTIONS, General, Hepatic).

DOSAGE AND ADMINISTRATION

The current insulin dose should be continued upon initiation of Rezulin therapy. Rezulin therapy should be initiated at 200 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Rezulin should be increased after approximately 2 to 4 weeks. The usual dose of Rezulin is 400 mg once daily. The maximum recommended daily dose is 600 mg. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and Rezulin. Further adjustments should be individualized based on glucose-lowering response. Rezulin should be taken with a meal.

Patients With Renal Insufficiency

Dose adjustment in patients with renal insufficiency is not required (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Patients With Hepatic Impairment

Rezulin should be used with caution in patients with hepatic disease (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

HOW SUPPLIED

Rezulin is available in 200 and 400 mg tablets as follows:

200 mg Tablets: Yellow, oval, non-scored, film-coated tablet with "PD 352" debossed on one side, and "200" on the other, available in:

N 0071-0352-15 Bottles of 30

N 0071-0352-23 Bottles of 90

N 0071-0352-40 (10 x 10 unit-dose blisters)

400 mg Tablets: Tan, oval, non-scored, film-coated tablet with "PD 353" debossed on one side, and "400" on the other, available in:

N 0071-0353-15 Bottles of 30

N 0071-0353-23 Bottles of 90

N 0071-0353-40 (10 x 10 unit-dose blisters)

Storage

Store at controlled room temperature 20°C-25°C (68°F-77°F). Protect from moisture and humidity.

Caution: Federal law prohibits dispensing without prescription.

©1997, Warner-Lambert Co.

January 1997

PARKE-DAVIS

Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

Marketed by:

PARKE-DAVIS

Div of Warner-Lambert Co and

SANKYO PARKE DAVIS

Parsippany, NJ 07054 USA



CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER: 20720, S01, S02, S03, S04, S05,
S06, S07**

MEDICAL REVIEW(S)

NOV 19 1997

MEDICAL OFFICER' REVIEW

NDA 20-720
REZULIN (TROGLITAZONE)
SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED
SUBMISSION OF OCTOBER 28, 1997

TROGLITAZONE HEPATOTOXICITY

APPROPRIATE COPY
OF ORIGINAL

Following extensive consultation with DMEDP Parke-Davis has revised its labeling to reflect post-marketing reports of irreversible liver injury in patients taking troglitazone. The action taken and changes being effected as are follows:

- 1 Direct mailing of "Dear Dr" letter on Friday October 31, with a warning about liver injury in patients on troglitazone
- 2 Changes in the label, warning of hepatic failure including death in bold type
- 3 Recommendation for monitoring of liver enzymes at 1-2 months after initiation of therapy and every three months thereafter for the first year.
- 4 Recommendation that troglitazone be discontinued if there is evidence of hepatic injury- jaundice and/or ALT greater than 3x upper limit of normal

Details of these cases of liver injury and other background material are presented below.

Post-marketing experience:

Total exposure to troglitazone is approximately 650,000 (500,000 USA and 150,000 Japan), although only about 100,000 have been taking the drug for over six months. There are well documented reports of 20 cases of serious hepatic events associated with the use of troglitazone. There were six cases from Japan, one from Puerto Rico and the rest from the United States. There has been one death due to hepatic failure and one liver transplant. An additional patient was scheduled to have a liver transplant but is now improving. Six patients have been reported to have recovered. The outcome is unknown in three cases and the rest are described as "improving" or "not fully recovered". With the exception of one atypical case in which hyperbilirubinemia was reported after a few days of treatment, all the other cases were reported between 1 and 6 months after initiation of treatment with a median of three months. The abnormality does not appear to

be dose-dependent. Liver biopsies were described as showing necrosis with bridging. All patients were known to have had normal liver enzymes before treatment.

In addition to the 20 well-documented cases described above, there are 19 cases which are poorly documented, or are associated with other factors which appear to be more likely explanations for liver dysfunction than troglitazone (one case was obstructive jaundice with pancreatic cancer).

Evidence of Liver Dysfunction in the Troglitazone NDA

As of February 3 (from submission of October 21, 1997) Parke-Davis reported 21 patients with treatment-emergent elevations of transaminases greater than 3x normal which required troglitazone to be discontinued. The maximum ALT exceeded 10x ULN (over 350 U/L) in 13/21 cases and exceeded 1000 in 5/21 cases. There are three cases of biopsy proven hepatitis with peak transaminase levels of 1000 U/L and jaundice in two cases. The onset of the first diagnosable liver abnormality occurred on days 85, 173, and 244 of the study. The abnormalities resolved after troglitazone was discontinued. There were also 17 cases with ALT greater than 3x normal (3 of which were greater than 10x normal) in which the ALT returned to normal despite continuation of troglitazone treatment.

Total exposure to troglitazone in clinical trials was 2519 patients, with 1725 patients exposed for 85 days or longer. Thus a reasonable estimate of the frequency of development of a transaminase over 3x normal is about 1.9% with an ALT over 1000 in 0.4%. Approximately 0.1% were reported to have developed jaundice but no patient had irreversible liver damage. The incidence of transaminase over 3x normal in 475 placebo-treated patients was 0.6%. There was no case of a transaminase over 10x normal.

Evidence of Liver Dysfunction in NDA's for other oral antidiabetic agents:

For establishing criteria for diagnosis of troglitazone hepatotoxicity it is necessary to know the frequency of abnormal transaminases in the diabetic population. I have therefore examined the data bases from USA placebo-controlled phase 3 studies of miglitol, acarbose and metformin to help provide some estimate of the proportion of patients who develop asymptomatic increase in transaminases which were not found to progress to clinically significant liver disease. In miglitol studies, 3/545 (0.6%) patients on placebo developed an increase in any LFT of

>3xULN. With acarbose, 3/865(0.3%) had SGOT>3xULN and 5/865 (0.6) had SGPT >3xULN. Among only type 2 patients on insulin, 0/237 had SGOT > 3x ULN and 2/237 (0.8%) had SGPT > 3xULN. Even among these insulin-treated patients, the highest SGPT was 3.69xULN. In the metformin studies of 921 patients, 7 had an elevated SGOT at baseline but all were less 2xULN. During the 29 week studies, 4 patients (0.4%), one patient in each active treatment group, developed SGOT >3xULN. No patient in the placebo group developed SGOT >3xULN The highest SGOT was 249 in a patient on glyburide which was felt to be a lab error because it was normal when repeated. On case was attributed to Voltaran and one to definite exposure to non-A non B hepatitis. As was true of the other studies, SGPT tended to be higher than SGOT.

In summary, these data bases, comprising 2331 type 2 diabetic patients receiving placebo in controlled trials with serial monitoring of liver enzymes are all consistent and lead to the conclusions that only about 0.6% will have an ALT over 3xULN at some point during treatment. No case of severe or prolonged liver disease was reported.

BASIS FOR MONITORING

Among the three patients with jaundice and/or biopsy-proven troglitazone-associated hepatitis in the phase 3 trials, the minimal enzyme elevation which would have permitted early diagnosis was ALT of 4.1xULN (140 U/l). This abnormality occurred 28 and 63 days before the onset of jaundice in the two patients who developed jaundice. Thus, setting a value of >3x ULN for ALT would cover all cases of troglitazone associated hepatitis which is about 2% of all patients treated. We know that the non-specific elevation in ALT over 3x normal observed in patients with diabetes is about 0.6%. Thus discontinuation of troglitazone treatment for ALT elevation would be expected to prevent progression of liver injury in all patients with troglitazone associated hepatitis while depriving very few patients of this drug because of a non-specific ALT elevation which occurs even without drug therapy. 98% of patients would continue to take troglitazone.

/S/

Robert I Misbin MD
Medical Officer
November 12, 1997
NDA 20-720/
HFD 510:misbin/fleming/sobel/bilstad/johnston

nic verner

/S/

11/13/97

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER: 20720, S01, S02, S03, S04, S05,
S06, S07**

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW		JUL 16 1997
1. ORGANIZATION CDER/HFD-510 Division of Metabolism and Endocrine Drug Products		2. NDA # 20-720 Approved: 29-JAN-1997
3. NAME AND ADDRESS OF APPLICANT Parke-Davis Pharmaceutical Research Division Warner-Lambert Company 2800 Plymouth Road P.O. Box 1047 Ann Arbor, MI 48106-1047 (313) 966-5000		4. SUPPLEMENT SCS-005 Doc. 17-JUN-1997 Rec. 19-JUN-1997
		5. Name of the Drug Rezulin
		6. Nonproprietary Name Troglitazone
7. SUPPLEMENT PROVIDES for a new tablet dosage strength, 300 mg, in addition to the approved 200 and 400 mg tablet strengths.		8. AMENDMENT Doc. 08-JUL-1997 (Ref. 63)
9. PHARMACOLOGICAL CATEGORY Hypoglycemic Agent, NIDDM.	10. HOW DISPENSED R	11. RELATED -N. A. -
12. DOSAGE FORM Tablet	13. POTENCY 200, 300 and 400 mg	
14. CHEMICAL NAME AND STRUCTURE Troglitazone $C_{24}H_{27}NO_3S$ M.W. = 441.54 CAS No 97322-87-7 (1:1:1 stereoisomer mixture) (±)-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-thiazolidinedione		
15. COMMENTS This supplement seeks approval of a new tablet dosage strength, 300 mg. The new 300 mg strength tablets as the approved 200 mg and 400 mg tablets. These differ in the colorant (or the lack of it) employed.		
Although no stability data has been provided, the 300 mg tablets 200 mg and 400 mg strength tablets. Analytical release data from the 300-mg tablets 200- and 400-mg tablets.		
16. CONCLUSIONS AND RECOMMENDATIONS From the chemistry viewpoint this supplement can be approved. Issue Approval letter.		
17. REVIEWER NAME (AND SIGNATURE) Xavier Ysern, PhD /S/		DATE COMPLETED 08-JUL-1997
R/D INITIATED BY /S/ 7/16/97		filename: 20720s05.nda
DISTRIBUTION: Original: <input checked="" type="checkbox"/> NDA 20-720 cc: <input checked="" type="checkbox"/> HFD-510 Division File <input checked="" type="checkbox"/> CSO <input checked="" type="checkbox"/> Reviewer		

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER: 20720, S01, S02, S03, S04,
S05, S06, S07**

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-720 ref.# 39

Troglitazone
200, 400 mg tablets

MAR 13 1997

(Rezulin[®])

Submission Date: 2/25/97

Sponsor: Parke-Davis

Type of Submission: Labeling Supplement

Reviewer: Michael J. Fossler, Pharm. D., Ph. D.

Submission

The submission to NDA 20-720 contains labeling changes to the CLINICAL PHARMACOLOGY and Drug Interactions sections of the labeling for troglitazone tablets. Also included in the supplement is a study report examining the effects of troglitazone 400 mg daily for 10 days on the steady-state pharmacokinetics of digoxin. As troglitazone has been shown to be a potent inducer of CYP3A4, patients taking digoxin who are started on troglitazone might be expected to have decreased steady-state levels of digoxin.

Protocol

A summary of the study design is attached. Briefly, the study is an open-label, sequential study in 12 normal volunteers. Each subject was given 0.25 mg digoxin daily for 10 days, with serum digoxin levels evaluated on Day 10. Each subject was then started on troglitazone 400 mg daily along with digoxin for an additional 10 days with serum levels of digoxin evaluated on Day 20. Urine was also collected on days 10 and 20 in order to determine the amount of digoxin excreted in the urine. Trough (pre-dose) levels of both digoxin and troglitazone were taken as well to verify the attainment of steady state.

Results

A summary of the results is presented in Table 1 below. Figure 1 depicts the mean steady-state digoxin levels before and after starting troglitazone.

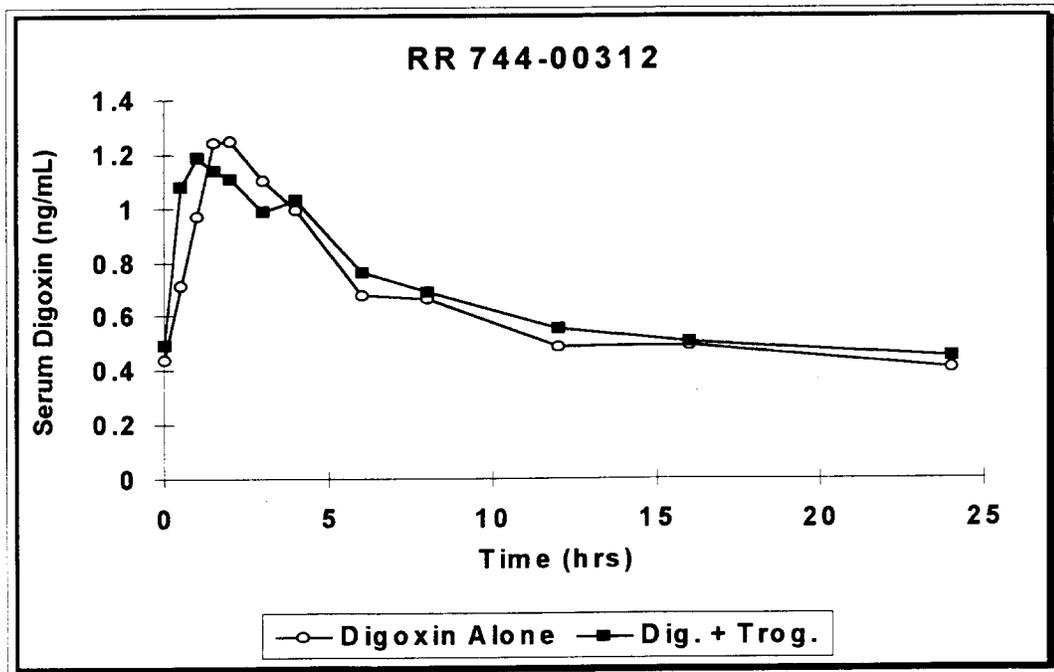
Table 1: Mean results of digoxin-troglitazone study.

Parameter	Treatment Mean \pm SD		Mean Ratios (95% CI)
	Digoxin (n = 11)	Digoxin + Troglitazone (n = 11)	
Cmax (ng/mL)	1.43 \pm 0.27	1.52 \pm 0.44	105 (86.5, 126) [‡]
tmax (hrs)	2.0 \pm 0.7	1.9 \pm 1.2	na
AUC(0-24 hrs) (ng•hrs/mL)	15.2 \pm 3.7	15.8 \pm 3.2	105 (95.1, 115) [‡]
*Ae(0-24 hrs) (μ g)	123 \pm 31	141 \pm 22	115 (102, 127)
Clrenal (mL/min)	142 \pm 47	154 \pm 38	108 (96.6, 120)

[‡] performed on log-transformed data

*Ae: amount excreted in the urine over 24 hrs

Figure 1: Mean steady-state concentrations of digoxin with and without concomitant troglitazone (n = 11).



Reviewer Comments

1) The relatively large difference in amount excreted (Ae) between treatment arms seen in Table 1 is due primarily to one subject (#6) having an unusually low Ae value during the digoxin-only arm. During the second arm of the study (digoxin + troglitazone) the Ae value for this subject was in line with the other subjects. It is unknown why this occurred, but it is likely that some urine samples were lost, as the AUC(0-24) values for this subject for both treatments are not very different.

2) Overall, there does not appear to be an interaction between digoxin and troglitazone. This result, at first glance is puzzling, since digoxin has been shown to interact with 3A4 substrates such as erythromycin, cyclosporin, itraconazole and ketoconazole¹. However, there may be other explanations for the increase in serum digoxin following 3A4 inhibitors. Erythromycin may act to increase digoxin concentrations by killing intestinal bacteria that break down digoxin in the GI tract. The interaction between cimetidine (which inhibits many other P450 isozymes in addition to 3A4) is very minor and may not exist at all.²

3) The firm's labeling regarding the results of this study is as follows:

Digoxin: Coadministration of Rezulin with digoxin does not alter the steady-state pharmacokinetics of digoxin.

This appears to be appropriate given the results of the study.

¹Digoxin is 50-80% renally excreted, with the balance thought to be hepatically eliminated.

²Source: Micromedex, Vol. 29

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (HFD-870) has reviewed the submission to NDA 20-720 thoroughly. Based on that review, OCPB agrees that there does not appear to be an interaction between digoxin and troglitazone. The proposed labeling resulting from the study is acceptable. OCPB has no comments to the firm at this time.

2/13/97

Michael J. Fossler, Pharm. D., Ph. D.

Division of Pharmaceutical Evaluation II

Office of Clinical Pharmacology and Biopharmaceutics

FT initialed by Hae-Young Ahn, Ph. D., Team Leader _____,

3/13/97

CC: NDA 20-720 (orig., 1 copy), HFD-510(Johnston, Fleming, Misbin), HFD-850(Lesko), HFD-870(M. Chen, Fossler, Ahn), Central Document Room (Barbara Murphy)

3/2/97

"CM"

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-720

Troglitazone
300 mg tablets

JUL 7 1997

(Rezulin[®])

Submission Date: 6/17/97

Sponsor: Parke-Davis

Type of Submission: NDA Supplement: New Dosage strength

Reviewer: Michael J. Fossler, Pharm. D., Ph. D.

Submission

The supplement to NDA 20-720 dated 6/17/97 is for troglitazone, presently indicated, either as monotherapy, or in combination with insulin or sulfonylureas, as an adjunct to diet and exercise to lower blood glucose in patients with Type II diabetes. The compound is marketed presently as 200 and 400 mg tablets. The recommended initial dose is 200 mg with breakfast. The maximum recommended dose is 600 mg daily.

The firm has developed a 300 mg tablet in order to make it more convenient to give 600 mg daily. No bioavailability data for the 300 mg tablet were included in the submission.

Table 1: Comparison of formulations of the 200, 300, and 400 mg troglitazone tablets.

Ingredient	Amount per 200 mg tablet (mg)	Amount per 300 mg tablet (mg)	Amount per 400 mg tablet (mg)
Troglitazone			
<i>Composed of:</i>			
<i>Troglitazone</i>	200.00	300.00	400.00
<i>Povidone</i>			
<i>Hydroxypropyl Methylcellulose,</i>			
<i>Polysorbate 80</i>			
<i>Polyethylene Glycol 400,</i>			
<i>Purified Water,</i>			
Croscarmellose Sodium			
Microcrystalline Cellulose			
Silicon Dioxide			
Magnesium Stearate			

AD 100

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (HFD-870) has reviewed the supplement to NDA 20-720 dated 6/17/97 and has concluded that the proposed 300 mg dosage form meets the criteria for a waiver of evidence of *in vivo* bioavailability under 21 CFR §320.22(d)(2)(i-iii). Accordingly, OCPB recommends approval of this tablet strength.

/S/

7/7/97

Michael J. Fossler, Pharm. D., Ph. D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/

FT initialed by Hae-Young Ahn, Ph. D., Team Leader

CC: NDA 20-720 (orig., 1 copy), HFD-510(Johnston, Ysern, Misbin), HFD-850(Lesko), HFD-870(M. Chen, Ahn), Central Document Room (Barbara Murphy)
3/2/97

" CM "

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER: 20720, S01, S02, S03, S04, S05,
S06, S07**

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

ORIGINAL



April 29, 1997

 NDA 20-720
Rezulin™
(troglitazone) Tablets



Re: Periodic ADE Submission

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857



Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the first quarterly periodic ADE report for Rezulin™ (troglitazone) Tablets, NDA 20-720, which was approved by the Agency on January 29, 1997.

This submission includes information on:

Initial Serious, Labeled Reports	0	Follow-Up Serious, Labeled Reports	0
Initial Non Serious Reports	18	Follow-Up Non Serious Reports	0
Initial 15-Day Alert Reports	2	Follow-Up 15-Day Alert Reports	0
Increased Frequency Reports	0		

Notes N.A.I. /S/ 5/8/97

As agreed upon during the March 25, 1997, telephone conversation between Rose Rogan, M.D., Vice President, Drug Safety Surveillance, Parke-Davis, and David Barash, RPH Chief, Division of Epidemiology and Surveillance, Food and Drug Administration, the time period covered by this report is January 30, 1997 to March 31, 1997.

MAI /S/ 5/12/97

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
	<input type="checkbox"/> MEMO
<i>/S/</i>	<i>5-20-97</i>
CSO INITIALS	DATE

Sincerely,

Mayra Ballina
Mayra Ballina, M.D.
Drug Safety Surveillance Physician
Worldwide Regulatory Affairs

bb
t:\nda\20-720\41097.dss

Attachments

Notes /S/ 5/19/97

ORIGINAL

*P-001
DEU-510*



July 30, 1997

NDA 20-720
- Rezulin™
(troglitazone) Tablets

Re: Periodic ADE Submission

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852-1833



Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the second quarterly periodic ADE report for Rezulin™ (troglitazone) Tablets, NDA 20-720, which was approved by the Agency on January 29, 1997.

This submission includes information on:

Initial Serious, Labeled Reports	6	Follow-Up Serious, Labeled Reports	0
Initial Non Serious Reports	249	Follow-Up Non Serious Reports	2
Initial 15-Day Alert Reports	30	Follow-Up 15-Day Alert Reports	15

Noted N.A.F. /S/ 8/18/97

The time period covered by this report is April 1, 1997 to June 30, 1997.

Included with the Periodic Report is a Transmittal of the Periodic Report Document. This document is to be signed, date stamped, and returned in the self-addressed, stamped envelope provided.

VPF /S/ 8/18/97

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
<i>/S/</i> <u>8-19-97</u>
CSO INITIALS DATE

Sincerely,

Mayra Ballina
Mayra Ballina, M.D.
Drug Safety Surveillance Physician
Worldwide Regulatory Affairs

bb
t:\nda\20-720\72497dss.doc

Attachments

Noted /S/ 8/18/97

ORIGINAL

P-002

Div-510

Pharmaceutica
Research

2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

ORIGINAL



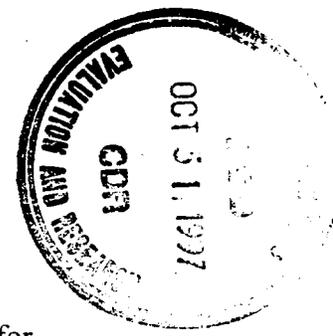
October 30, 1997

*Noted
1/S/
11/13/97*

= NDA 20-720
Rezulin™
(troglitazone) Tablets

Re: Periodic ADE Submission

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852-1833



Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the third quarterly periodic ADE report for Rezulin™ (troglitazone) Tablets, NDA 20-720, which was approved by the Agency on January 29, 1997.

This submission includes information on:

Initial Serious, Labeled Reports	3	Follow-Up Serious, Labeled Reports	1
Initial Non Serious Reports	331	Follow-Up Non Serious Reports	53
Initial 15-Day Alert Reports	87	Follow-Up 15-Day Alert Reports	40

The time period covered by this report is July 1, 1997 to September 30, 1997.

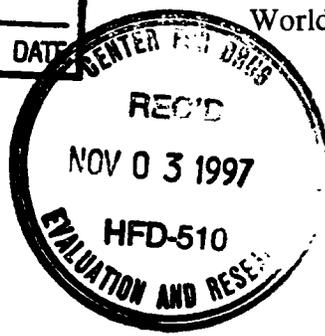
Included with the Periodic Report is a Transmittal of the Periodic Report Document. This document is to be signed, date stamped, and returned in the self-addressed, stamped envelope provided.

Sincerely,

*Noted
1/S/
11/13/97*

James Crook
James Crook, M.D., Ph.D.
Drug Safety Surveillance Physician
Worldwide Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
<input type="checkbox"/> MEMO	
CSO INITIALS	DATE



bb
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Attachments

ORIGINAL
12-003
DEC-510

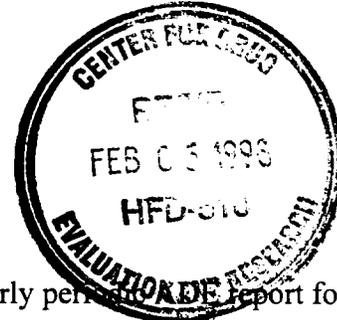


January 30, 1998

NDA 20-720
- Rezulin®
(troglitazone) Tablets

Re: Periodic ADE Submission

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852-1833



*Noted
/S/
2/5/98*

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the fourth quarterly periodic report for Rezulin® (troglitazone) Tablets, NDA 20-720, which was approved by the Agency on January 29, 1997.

This submission includes information on:

Initial Serious, Labeled Reports	43	Follow-Up Serious, Labeled Reports	1
Initial Non Serious Reports	416	Follow-Up Non Serious Reports	81
Initial 15-Day Alert Reports	314	Follow-Up 15-Day Alert Reports	43

*Noted
/S/
4/5/97*

The time period covered by this report is October 1, 1997 to December 31, 1997.

Included with the Periodic Report is a Transmittal of the Periodic Report Document. This document is to be signed, date stamped, and returned in the self-addressed, stamped envelope provided.

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.
<input type="checkbox"/> MEMO	
<i>/S/</i>	<i>2-5-98</i>
CSO INITIALS	DATE

Sincerely,

[Signature]
James Crook, M.D., Ph.D.
Drug Safety Surveillance Physician
Worldwide Regulatory Affairs

bb
t:\nda\20-720\013098ds.doc

Attachments

*No left
/S/
2/5/98*

ORIGINAL
*P - copy
Div-510*



March 16, 1998

NDA 20-720
Rezulin®
(troglitazone) Tablets

noted
1/31
4/13/98

Re: Correction to Periodic ADE Submission

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

Dear Sir or Madam:

Reference is made to our fourth quarterly periodic ADE report for Rezulin® (troglitazone) Tablets, NDA 20-720, which was submitted on January 30, 1998. The time period covered by the report was October 1, 1997 to December 31, 1997.



We are submitting herewith page 903, which was inadvertently omitted from the Rezulin fourth quarterly report. Please insert the attached page 903 into the Periodic ADE Submission dated January 30, 1998. We have added page 903 to our file copies. We apologize for any inconvenience this omission may have caused.

Included with this submission is a Transmittal of the Periodic Report Document. This document is to be signed, date stamped, and returned in the self-addressed, stamped envelope provided.

Please note that the area code and exchange numbers for my telephone and facsimile have changed effective immediately. If there are any questions or comments regarding this submission, please contact me at the new numbers of 734/622-7009 or via FAX at 734/622-2722.

M. Crook
1/31
1-10-98

Sincerely,

James Crook, M.D., Ph.D.
Drug Safety Surveillance Physician
Worldwide Regulatory Affairs

bb
t:\nda\20-720\021198ds.doc

Attachments

NAF
1/31
4-13-98



April 30, 1998

NDA 20-720

- Rezulin®
(troglitazone) Tablets

Re: Periodic ADE Submission

ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852-1833



Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the fifth quarterly periodic ADE report for Rezulin® (troglitazone) Tablets, NDA 20-720, which was approved by the Agency on January 29, 1997.

Handwritten initials: J.S.I.

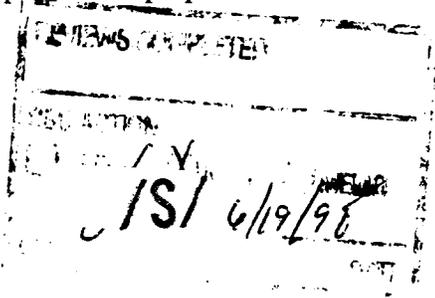
This submission includes information on:

Initial Serious, Labeled Reports	91	Follow-Up Serious, Labeled Reports	17
Initial Non Serious Reports	262	Follow-Up Non Serious Reports	116
Initial 15-Day Alert Reports	209	Follow-Up 15-Day Alert Reports	246

Handwritten date: 6/3/98

The time period covered by this report is January 1, 1998 to March 31, 1998.

Included with the Periodic Report is a Transmittal of the Periodic Report Document. This document is to be signed, date stamped, and returned in the self-addressed, stamped envelope provided.



Sincerely,

James Crook, M.D., Ph.D.
Drug Safety Surveillance Physician
Worldwide Regulatory Affairs

ORIGINAL

bb
t:\nda\20-720\042798-59611.doc

Attachments

Handwritten notes: JAT, 151, 5/18/98

Handwritten numbers: 0050, 1005

NOTE: This report is required by law (21 USC 355; 21 CFR 314.81). Failure to report can result in withdrawal of approval of the New Drug Application.

1. NDA OR ANDA NUMBER

N	2	0	7	2	0
---	---	---	---	---	---

2. Report No. (FDA Complete)
Y-

0	0	1
---	---	---

INSTRUCTIONS
Complete a transmittal form for each application for which an annual report is being submitted. Retain the carbon copy labeled "applicant." Submit the remaining copies of the transmittal form along with two copies of the annual report to FDA.
If any part of the annual report applies to more than one application, list in item 7 all other applications to which such parts apply.

APPLICANT NOTE:
Reference NDA and Y numbers (entered on Acknowledgment Copy) in any subsequent correspondence regarding report.

4. APPLICANT Parke-Davis Division of Warner-Lambert Company

3. CFR SECTION NUMBER (Antibiotic only)

5. DRUG NAME Rezulin Tablets, 200 & 400 mg (troglitazone)

6. TYPE OF REPORT (Check one)
 ANNUAL OTHER

7. OTHER NDA/ANTIBIOTIC APPLICATION NUMBERS (List all numbers if any part of report applies to more than one number.)

8. PERIOD COVERED BY REPORT

FROM		TO	
YEAR	MONTH	YEAR	MONTH
97	01	97	12

9. REPORT INFORMATION REQUIRED (See § 314.81 for description)
(Enter type of information attached under "Identification." If you have nothing to report, enter None.)
(INFORMATION IN "9b" and "9c" IS ALWAYS REQUIRED.)

TYPE OF INFORMATION	IDENTIFICATION (Volume No.(s)/Tab(s)/Page(s) of Report)
a. SUMMARY OF SIGNIFICANT NEW INFORMATION	Attached
b. DISTRIBUTION DATA	Attached
c. LABELING (Whether or not previously submitted)	Attached
d. CHEMISTRY MANUFACTURING AND CONTROLS CHANGES	Attached
e. NONCLINICAL LABORATORY STUDIES	None
f. CLINICAL DATA	Attached
g. STATUS REPORT POST-MARKETING STUDIES	Attached
h. STATUS OF OPEN REGULATORY BUSINESS (Optional)	None

Fold Line

Noted N.A.I. 1/5/98 4/13/98

Fold Line

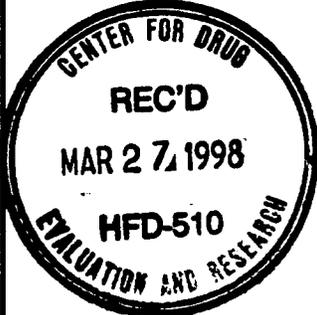
TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Sean Brennan, Ph.D.
Senior Director
Worldwide Regulatory Affairs

FDA USE ONLY
10. REPORT FILED IN NDA NUMBER

N	2	0	7	2	0
---	---	---	---	---	---

SIGNATURE *Phil Simonsen for STB.*

11. DATE OF RECEIPT



Noted 1/5/98 4/14/98

APPLICANTS RETURN ADDRESS (Type within the window envelope tic marks)

Sean Brennan, Ph.D.
Parke-Davis
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, Michigan 48105

NOTE: This report is required by law (21 USC 355; 21 CFR 314.81). Failure to report can result in withdrawal of approval of the New Drug Application.

INSTRUCTIONS

Complete a transmittal form for each application for which an annual report is being submitted. Retain the carbon copy labeled "applicant." Submit the remaining copies of the transmittal form along with two copies of the annual report to FDA.

If any part of the annual report applies to more than one application, list in item 7 all other applications to which such parts apply.

1. NDA OR ANDA NUMBER					
N	2	0	7	2	0
2. Report No. (FDA Complete)					
Y-	0	0	1		
<small>APPLICANT NOTE: Reference NDA and Y numbers (entered on Acknowledgment Copy) in any subsequent correspondence regarding report.</small>					
3. CFR SECTION NUMBER (Antibiotic only)					
6. TYPE OF REPORT (Check one) <input checked="" type="checkbox"/> ANNUAL <input type="checkbox"/> OTHER					
8. PERIOD COVERED BY REPORT					
<small>FROM</small>			<small>TO</small>		
<small>YEAR</small>	<small>MONTH</small>	<small>YEAR</small>	<small>MONTH</small>		
97	01	97	12		

4. APPLICANT Parke-Davis Division of Warner-Lambert Company

5. DRUG NAME Rezulin Tablets, 200 & 400 mg
(troglitazone)

7. OTHER NDA/ANTIBIOTIC APPLICATION NUMBERS *(List all numbers if any part of report applies to more than one number.)*

REPORT INFORMATION REQUIRED (See § 314.81 for description)
9. *(Enter type of information attached under "Identification." If you have nothing to report, enter None.)*
(INFORMATION IN "9b" and "9c" IS ALWAYS REQUIRED.)

TYPE OF INFORMATION	IDENTIFICATION <i>(Volume No.(s)/Tab(s)/Page(s) of Report)</i>
a. SUMMARY OF SIGNIFICANT NEW INFORMATION	Attached
b. DISTRIBUTION DATA	Attached
c. LABELING <i>(Whether or not previously submitted)</i>	Attached
d. CHEMISTRY MANUFACTURING AND CONTROLS CHANGES	Attached
e. NONCLINICAL LABORATORY STUDIES	None
f. CLINICAL DATA	Attached
g. STATUS REPORT POST-MARKETING STUDIES	Attached
h. STATUS OF OPEN REGULATORY BUSINESS <i>(Optional)</i>	None

REVIEW COMPLETED

CSO ACTION:

LETTER N.A.

7/5/ 7/20/98

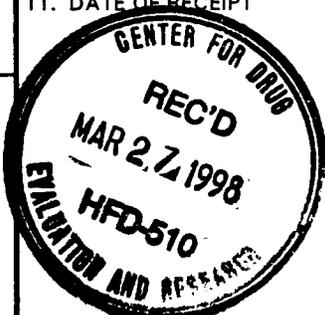
CSO INITIALS DATE

TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Sean Brennan, Ph.D.
Senior Director
Worldwide Regulatory Affairs

SIGNATURE
Phil Simmons for STB.

APPLICANTS RETURN ADDRESS *(Type within the window envelope tic marks)*

Sean Brennan, Ph.D.
Parke-Davis
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, Michigan 48105

FDA USE ONLY	
10. REPORT FILED IN NDA NUMBER	
N	2 0 7 2 0
11. DATE OF RECEIPT	
	



Food and Drug Administration
Rockville MD 20857

NDA 20-720/S-001

JUN 2 1997

Parke Davis Pharmaceutical Research
Attention: James A. Parker, Jr.
Director, Advertising and Labeling
Worldwide Regulatory Affairs
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Parker:

We acknowledge the receipt of your April 22, 1997, submission containing final printed labeling (FPL) in response to our January 29, 1997, letter approving your new drug application for Rezulin™ (troglitazone) Tablets, 200 mg and 400 mg. Please note that the package insert provided with this final printed labeling submission incorporates changes approved in supplement-001 approved on April 4, 1997 but does not incorporate changes approved in supplement-004 on that same date.

We have reviewed the labeling that you have submitted in accordance with the S-001 approval in our April 4, 1997 letter, and we find it acceptable.

Sincerely yours,

IS/ 5-29-97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug
Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPROVED FOR SIGNATURE
MAY 1997

cc:

Original NDA 20-720
HFD-510/Div. Files
HF-2/Medwatch (with labeling) —
HFD-102/Office Director (with labeling)
HFD-510/MJohnston
HFD-40/DDMAC (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)

APPROPRIATE COPY
OF ORIGINAL

Drafted by: Mjohnston 5.2.97/C:\wpfiles\n20720\s001ar
Initialed by: Rmisbin5.2.97/AFleming5.2.97/XYsern5.5.97/SMoore5.5.97/HRhee5.6.97/
Rsteigerwalt5.7.97/MFossler5.8.97/HAhn5.29.97/Egalliers5.29.97
final: Mjohnston5.29.97

ACKNOWLEDGE AND RETAIN (AR)

APPROPRIATE COPY
OF ORIGINAL



April 22, 1997

NDA 20-720
Ref. No. 47
Rezulin™ (troglitazone) Tablets

Re: Final Printed Labeling

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Sobel:

Reference is made to our approved NDA for Rezulin™ (troglitazone) tablets. Reference is also made to the approval letter, dated January 29, 1997, which requested the submission of twenty copies of the Final Printed Labeling (FPL).

In accordance with your request we are providing the following FPL:

	<u>Item</u>	<u>Specification Number</u>
Attachment 1:	200 mg Bottle Label/30's	0352G030
Attachment 2:	200 mg Bottle Label/90's	0352G070
Attachment 3:	200 mg SAMPLE/30's	0352G130
	200 mg Sample 4 X 7's:	
Attachment 4:	Blister Card	0352C070
Attachment 5:	Primary Carton	0352C060
Attachment 6:	Detailer Container	0352C050
Attachment 7:	400 mg Bottle Label/30's	0353G030
Attachment 8:	400 mg Bottle Label/90's	0353G050
Attachment 9:	400 mg SAMPLE/30's	0353G110
	400 mg Sample 4 X 7's:	
Attachment 10:	Blister Card	0353C070
Attachment 11:	Primary Carton	0353C060
Attachment 12:	Detailer Container	0353C050
Attachment 13:	Package Insert	0352G041

Solomon Sobel, M.D.

NDA 20-720

April 22, 1997

Page 2

SEARCHED
SERIALIZED

If you have any questions or require additional information, please do not hesitate to contact me at 201/540-3113 or FAX 201/540-5972.

REVIEWS COMPLETED	
CSU	
CSO ACTION: AR L+r	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
6-29-97	
IS/	DATE

Sincerely,



James A. Parker, Jr.
Director, Advertising and Labeling
Worldwide Regulatory Affairs

c:\data\wpdocs\rezulin\fp10418.97

SEARCHED
SERIALIZED

CSO REVIEW OF REVISED PACKAGE INSERT

ORIGINAL

MAY 29 1997

NDA 20-720/S-001

Troglitazone 200 mg and 400 mg tablets

Reviewed: May 1, 1997 by Michael F. Johnston, Project Manager

Labeling Pieces Reviewed: Unless noted below (items #3, #6, #9, #12) fpl (listed below) submitted on April 22, 1997 vs. original NDA approved container labeling submitted on January 22, 1997, with the exception of package insert (see note under #13 below)

1. 200 mg Bottle Label / 30's (#0352G030):

Changes Noted: None

2. 200 mg Bottle Label / 90's (#0352G070):

Changes Noted: None

3. 200 mg Sample / 30's (#0352G130):

Changes Noted: Not submitted with original NDA. Only change from #1 above is addition of phrase: "Professional Sample-Not to be sold."

4. 200 mg Sample 4 X 7's (Blister Card)(#0352G070):

Changes Noted: None

5. 200 mg Sample 4 X 7's (Primary Carton)(# 0352C070):

Changes Noted: None

6. 200 mg Sample 4 X 7's (Detailer Container)(0352C050):

Changes Noted: Not submitted with original NDA. Information is identical to that contained on #5 except for quantity designation of "4 PROFESSIONAL SAMPLES (7 tablets each)"

7. 400 mg Bottle Label / 30's (#0353G030):

Changes Noted: None

8. 400 mg Bottle Label / 90's (#0353G050):

Changes Noted: None

9. 400 mg Sample 30's (#0353G110):

Changes Noted: Not submitted with original NDA. Only change from #8 above is addition of phrase: "Professional Sample-Not to be sold."

10. 400 mg Sample 4 X 7's (Blister Card)(#0353C070):

Changes Noted: None

11. 400 mg Sample 4 X 7's (Primary Carton)(#0353C060):

Changes Noted: None

12. 400 mg Sample 4 X 7's (Detailer Container)(#0353C050):

Changes Noted: Not submitted with original NDA. Only change from #11 above is addition of phrase: "Professional Sample-Not to be sold."

13. Package Insert (0353G041): Comparison between draft package insert, version 7 (with handwritten changes submitted immediately prior to approval), submitted on 1/29/97 and label version dated January, 1997 (serial #0352G041) submitted as S-001 on January 31, 1997. This label was expedited to provide for the last minute drug interaction information in Rezulin labels being printed for the product release. fpl package insert in this submission has now been superseded by labeling reviewed in S001 and S004 and approved April 4, 1997. This draft package insert version was also reviewed in the labeling review of April 1, 1997.

Changes Noted:

A. In the CLINICAL PHARMACOLOGY/Metabolism section: (third paragraph)

Deletes word "nevertheless" from sentence: "The results of *in vivo* drug interaction studies tend to support this observation (see **Drug Interactions**); caution should be observed when Rezulin is used in combination with drugs known to be metabolized by one of these enzymes.

B. In the PRECAUTIONS/Drug Interactions:

Adds the following new sections:

Terfenadine: Coadministration of Rezulin with terfenadine decreases plasma concentration of terfenadine and its active metabolite by 50-70% and may reduce the effectiveness of terfenadine.

Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl-estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%. These changes could result in the loss of contraception.

The above interaction with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. These findings should be considered when prescribing other CYP3A4 substrates such as cyclosporin, tacrolimus, and some HMG-CoA reductase inhibitors.

NDA 20-720/S-001

Troglitazone 200 mg and 400 mg tablets

Reviewed: May 1, 1997 by Michael F. Johnston, Project Manager

Labeling Pieces Reviewed: Unless noted below (items #3, #6, #9, #12) fpl (listed below) submitted on April 22, 1997 vs. original NDA approved container labeling submitted on January 22, 1997, with the exception of package insert (see note under #13 below)

REVIEWERS NOTE: Please sign below (in addition to routing slip)

IS/ 5/1/97
MO signature/date

IS/ 5/5/97
MO GpLdr signature/date

IS/ 5/5/97
Chemistry Reviewer

IS/ 5/5/97
Chemistry Team Ldr.

IS/ 5/7/97
Pharmacology Reviewer

IS/ 5/7/97
Pharmacology Team Ldr.

IS/ 5/8/97
Biopharm Reviewer

IS/ 5/29/97
Biopharm Team Ldr

IS/ 5/2/97
CSO Reviewer/date

IS/ 5/29/97
SCSO/date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA File: NDA 20-720
HFD-510: MJohnston



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date FEB 24 1997

NDA No. 20-720

PARKE-DAVIS PHARMACEUTICALS RESEARCH
2800 Plymouth Road
Ann Arbor, MI 48105

Attention: Irwin G. Martin, Ph.D., Vice President, FDA Liaison, Worldwide
Regulatory Affairs

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: REZULIN (troglitazone) Tablets

NDA Number: 20-720

Supplement Number: S-001

Date of Supplement: January 31, 1997

Date of Receipt: February 3, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the
Act on APR 4 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

/S/

Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office Drug Evaluation II
Center for Drug Evaluation and Research

Pharmaceutical
Research

1800 Plymouth Road
Ann Arbor, MI
48105

Phone: (313) 996-7756
Facsimile: (313) 998-2856
E-Mail: martin@aa.wl.com

NDA SUPPLEMENT ORIGINAL

NDA NO. 20-720 REF. NO. 34
NDA SUPPL FOR SLR



Irwin G. Martin, Ph.D.
Vice President, FDA Liaison
Worldwide Regulatory Affairs

January 31, 1997

- NDA 20-720
Ref. No. 34
Rezulin™ (troglitazone) Tablets

Re: Special Supplement
Changes Being Effected

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Sobel:

Reference is made to our approved NDA 20-720 for Rezulin™ (troglitazone) Tablets.

Additional reference is made to our teleconference with members of your Division on this date. As Parke-Davis learned today of an interaction between troglitazone and oral contraceptives, the PRECAUTIONS, Drug Interactions has been updated pursuant to 21 CFR 314.70(c)(2)(i). A minor deletion in CLINICAL PHARMACOLOGY, Metabolism, has also been made.

A summary of the new data as well as copies of the revised label are attached.

Should you have any questions regarding this submission, please contact me at 313/996-7756 or FAX 313/998-2856.

Sincerely,

Irwin G. Martin

REVIEWS COMPLETED	
ACTION: A	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/	1/31/97
CSO INITIALS	DATE

IM\rm
t:\nda\20-720\013197.034

Attachment

NOTED,
CLPB WILL REVIEW
FULL STUDY REPORTS
WHEN THEY ARE SUBMITTED
POST-APPROVAL.
/S/ 2/14/97

Food and Drug Administration
Rockville MD 20857

NDA 20-720/S-004

JUL 31 1997

Parke Davis Pharmaceutical Research
Attention: James A. Parker, Jr.
Director, Advertising and Labeling
Worldwide Regulatory Affairs
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Parker:

We acknowledge the receipt of your June 17, 1997, submission containing final printed labeling (FPL) in response to our April 4, 1997, letter approving your supplemental new drug application for Rezulin™ (troglitazone) Tablets, 200 mg and 400 mg. We note that FPL for changes approved in supplement-001 was previously provided in your FPL submission dated April 22, 1997.

We have reviewed the labeling that you have submitted in accordance with our April 4, 1997 letter, and we find it acceptable.

Sincerely yours,

/S/7-31-97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug
Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-720
HFD-510/Div. Files
HF-2/Medwatch (with labeling)
HFD-510/MJohnston
HFD-40/DDMAC (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)

Drafted by: Mjohnston 6.24.97/C:\wpfiles\n20720\s004ar

Initialed by: Rmisbin6.31.97/AFleming7.1.97/XYsern6.30.97/SMoore6.30.97/
Hrhee7.22.97/RSteigerwalt7.22.97/Egalliers7.31.97

final: Mjohnston7.31.97

ACKNOWLEDGE AND RETAIN (AR)



June 17, 1997

NDA 20-720
Ref. No. 56
Rezulin™ (troglitazone) Tablets

Re: Final Printed Labeling for
Approved Supplemental NDA S-004

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Sobel:

Reference is made to our approved NDA for Rezulin™ (troglitazone) tablets. Reference is also made to our Supplemental NDA (S-004), submitted February 25, 1997, which provided for revisions to the CLINICAL PHARMACOLOGY, and PRECAUTIONS Sections of the package insert. Lastly, reference is made to your subsequent approval letter, dated April 4, 1997, in which you requested submission of twenty copies of the Final Printed Labeling (FPL).

In accordance with your request we are providing 20 copies of the package insert specification number 0352G042 as Attachment 1.

If you have any questions or require additional information, please do not hesitate to contact me at 201/540-5529 or FAX 201/540-5972.

REVIEWS COMPLETED	
CSO ACTION:	AR
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/	7-31-97
CSO INITIALS	DATE

Sincerely,

Patricia A. Carlson
Manager, Advertising and Labeling
Worldwide Regulatory Affairs

PC\sv\rm
t:\nda\20-720\061697-056

Attachment

CSO REVIEW OF REVISED PACKAGE INSERT

ORIGINAL

NDA 20-720/S-001 and 20-719/S-001

Ref: P-D Ltr of February 20, 1997 (Grants Cross Reference to Sanyo U.S.A)

Troglitazone 200 mg and 400 mg tablets

Reviewed: April 1, 1997 by Michael F. Johnston, CSO

Labeling Pieces Reviewed: Comparison between draft package insert, version 7 (with handwritten changes submitted immediately prior to approval), submitted on 1/29/97 and label version dated January, 1997 (serial #0352G041) submitted as S-001 on January 31, 1997. This label was expedited to provide for the last minute drug interaction information in Rezulin labels being printed for the product release.

Changes Noted:

1. In the CLINICAL PHARMACOLOGY/Metabolism section: (third paragraph)

Deletes word "nevertheless" from sentence: "The results of *in vivo* drug interaction studies tend to support this observation (see **Drug Interactions**); caution should be observed when Rezulin is used in combination with drugs known to be metabolized by one of these enzymes.

2. In the PRECAUTIONS/Drug Interactions:

Adds the following new sections:

Terfenadine: Coadministration of Rezulin with terfenadine decreases plasma concentration of terfenadine and its active metabolite by 50-70% and may reduce the effectiveness of terfenadine.

Oral Contraceptives: Administration of Rezulin with an oral contraceptive containing ethinyl-estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%. These changes could result in the loss of contraception.

The above interaction with terfenadine and oral contraceptives suggest that troglitazone may induce drug metabolism by CYP3A4. These findings should be considered when prescribing other CYP3A4 substrates such as cyclosporin, tacrolimus, and some HMG-CoA reductase inhibitors.

CSO REVIEW OF REVISED PACKAGE INSERT

NDA 20-720/S-004 and 20-719/S-004

Ref: P-D Ltr of February 20, 1997 (Grants Cross Reference to Sanyo U.S.A)

Troglitazone 200 mg and 400 mg tablets

Reviewed: April 2, 1997 by Michael F. Johnston, CSO

Labeling Pieces Reviewed: Comparison between label version submitted on January 31, 1997 in supplement #001 [Edition dated January, 1997 (serial #0352G041)] and version submitted on February 25, 1996 in supplement #004 (Three column explanatory labeling labeled "January, 1997"). Note: The supplement #004 label version implements changes, with some modifications, requested in a February 11, 1997 FDA telefax to Parke-Davis.

Changes Noted:

1. In the CLINICAL PHARMACOLOGY/Metabolism section: Rewords paragraph #2 and #3

Replacing it with:

Troglitazone incubated with expressed human P450 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, and 3A4 in the presence and absence of known inhibitors of these enzymes showed no Metabolite 3 formation above levels in control samples. Studies in human microsomes suggest that Metabolite 3 is not subject to further metabolism by the major P450 isozymes. Troglitazone did not inhibit any of the major P450 enzymes at clinically relevant concentrations. The inhibitory characteristics of Metabolite 3 have not been investigated directly.

The results of human *in vivo* drug interaction trials suggests that troglitazone induces cytochrome P450 3A4 at clinically relevant doses. (See **Drug Interactions**)

Note the differences in the third paragraph between the proposed P-D version and the version FAXed to P-D on Feb 11, 1997:

The results of human trials suggest that troglitazone induces cytochrome P450 3A4 at clinically relevant doses. Patients taking agents which are metabolized by this enzyme may show decreased efficacy after starting troglitazone (See **Drug Interactions**).

2. In the PRECAUTIONS/Drug Interactions section: Revises previous drug interaction section including: (See Attachment #1 for new wording and comparisons to FDA request of Feb 11, 1997)

A. In "Sulfonylurea" section: Changes section title from "Sulfonylurea" to "Glyburide." (FDA requested) Parke Davis proposes to retain statement: "glyburide does not appear to alter troglitazone or glyburide pharmacokinetics." (**Note wording change from FDA proposed language**)

B. Adds Digoxin interaction section: New report results showing no Rezulin effect on the steady state pharmacokinetics of digoxin.

C. In "Oral Contraception" section: Adds wording: "Therefore, a higher dose of oral contraceptive or an alternative method of contraception should be considered." (**Note: this varies from FDA proposed language**)

D. For "Terfenadine": changes terfenadine and active metabolite plasma concentrations decreased from 30% to 50-70%. (**note change from FDA version**)

E. Revises last two paragraphs in the Drug Interactions section to remove Digoxin, hydrochlorothiazide, and sulfonylureas. Digoxin comment (no interaction) moved to separate section. Hydrochlorothiazide is renally excreted and sulfonylureas are metabolized by CYP 2C9. (**Note: this is wording change from proposed FDA language**)

3. In the "PRECAUTIONS/Information for Patients" section: Adds paragraphs: (**Note: wording changes from FDA proposed language**)

Use of Rezulin can cause resumption of ovulation in women taking oral contraceptives and in patients with polycystic ovary disease. Therefore, a higher dose of an oral contraceptive or an alternative method of contraception should be considered.

Rezulin may affect other medications used in diabetic patients. Patients started on Rezulin should ask their physician to review their other medications to make sure that they are not affected by Rezulin.

ATTACHMENT

NDA 20-720/S-001 and 20-719/S-001
NDA 20-720/S-004 and 20-719/S-004

Review of Final Approved Labeling with Drug Interaction Chages

REVIEWERS NOTE: Please sign below (in addition to routing slip)

Handwritten: /S/ 2/2/97

<u>MO signature/date</u>	<u>MO GpLdr signature/date</u>
<i>/S/ 2/4/97</i>	<i>/S/ 3/10/97</i>
<u>Biopharm Reviewer</u>	<u>Biopharm Tm Ldr</u>
<i>/S/ 3/31/97</i>	<i>/S/ 4/2/97</i>
<u>CSO-Reviewer/date</u>	<u>SCSO/date</u>

cc: Original NDA File: NDA 20-720
Original NDA File: NDA 20-719
HFD-510: MJohnston/RMisbin/GFleming/MFossler/HAhn

MEMORANDUM OF EMAIL (encrypted Internet)

NDA 20-720

11 February 1997

Rezulin (troglitazone) Tablets

Parke-Davis

Mary Taylor, MPH

Director, Worldwide Regulatory Affairs

Based on FDA review of labeling Supplement-001 (S-001 was submitted under 21 CFR 314.70(c) as a CHANGE BEING EFFECTED per oral agreement with Dr. Sobel) and the accompanying study reports, we requested the applicant (by encrypted Internet mail) to make additional changes in the CLINICAL PHARMACOLOGY/Metabolism, the PRECAUTIONS/Information for Patients, and PRECAUTIONS/Drug Interactions sections of the product's labeling. The changes are highlighted in the attached, "marked-up" version of the package insert dated Feb. 11, 1997.

/S/

Enid Galliers for Michael Johnston, Project Manager**ATTACHMENT**

cc: Orig. NDA 20-720

HFD-510/Div. File

HFD-510/RMisbin/MFossler/MJohnston

drafted by Egalliers \20720sr.emg

SUPPLEMENT REQUEST



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date **MAR 3 1997**

NDA No. 20-720

PARKE-DAVIS PHARMACEUTICAL RESEARCH
DIVISION of WARNER-LAMBERT COMPANY
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

Attention: Mary E. Taylor, M.P.H., Director, Worldwide Regulatory Affairs

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: REZULIN (troglitazone) Tablets

NDA Number: 20-720

Supplement Number: S-004

Date of Supplement: February 25, 1997

Date of Receipt: February 26, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the
Act on APR 27 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

/S/

Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office Drug Evaluation II
Center for Drug Evaluation and Research

Pharmaceutical
Research

2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

NDA SUPPLEMENT

ORIGINAL



NDA NO. 20-720 REF. NO. 039

NDA SUPPL FOR Labeling

February 25, 1997

NDA 20-720

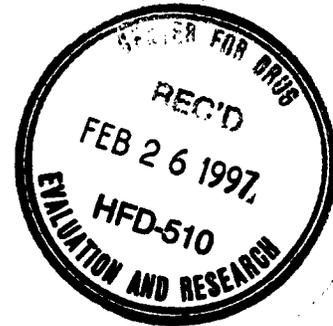
Ref. No. 039

Rezulin™ (troglitazone) Tablets

Re: Labeling Supplement

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Noted/S/
3/10/97



Dear Dr. Sobel:

Reference is made to our approved application for Rezulin™ (troglitazone) Tablets.

Reference is also made to your comments on our approved labeling provided by FAX on February 14, 1997. We have incorporated many of your comments and have modified others. Details are provided in the attached proposal (Attachment 1). The Drug Interaction section of the labeling is also updated to include results of the digoxin interaction study. Research report entitled, "A Study to Evaluate the Effects of Troglitazone (CI-991) on the Steady-State Pharmacokinetics of Digoxin in Healthy Volunteers (Protocol 991-087-0)" is submitted with this supplement (Attachment 2).

If there are any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

Sincerely,

Mary E. Taylor

Notes

Mary E. Taylor, M.P.H.
Director
Worldwide Regulatory Affairs

MT\rm t:\nda\20-720\022597.039

Attachments

Copies: "Blue" Archival
"Tan" Clinical
"Orange" Biopharmaceutics

REVIEWS COMPLETED	
GSO ACTION: <i>Noted</i>	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
<i>/S/</i>	<i>3/10/97</i>
GSO INITIALS	DATE

Desk Copy: M. Johnston, HFD-510 (Attachment 1 only)



Food and Drug Administration
Rockville MD 20857

NDA 20-720/S-005

PARKE-DAVIS PHARMACEUTICAL RESEARCH, Inc.
Attention: Sean Brennan, Sr. Director, Worldwide Regulatory Affairs
2800 Phymouth Road
Ann Arbor, MI 48105

JUN 27 1997

Dear Dr. Bennan:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: REZULIN (troglitazone) Tablets

NDA Number: 20-720

Supplement Number: S-005

Date of Supplement: June 17, 1997

Date of Receipt: June 19, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on August 18, 1997, in accordance with 21 CFR 314.101(a). Please note that this change dose not qualify for submission as a change being effected (21 CFR 314.70(c).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely

/S/

Enid Galliers'
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS DAY
IN THE FEDERAL REGISTER

NDA 20-720/S-005

Page 2

cc:

Original NDA 20-720/S-005

HFD-510/Div. Files

HFD-510/CSO/M.Jonhston

filename: C:\WPFILES\20720ACS.WPD

SUPPLEMENT ACKNOWLEDGEMENT



Sean Brennan, Ph.D.
Senior Director
Vice President, Regulatory Affairs

July 9, 1997

NDA 20-720
Ref. No. 064
Rezulin™ (troglitazone) Tablets

Re: Sankyo NDA Reference Permission

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Sobel:

Reference is made to our approved application for Rezulin™ (troglitazone) Tablets.

Permission is hereby granted to Sankyo U.S.A. Corporation to include by reference the complete contents of NDA 20-720, including supplement S-005 dated June 17, 1997.

If there are any questions or comments regarding this submission, please contact me at 313/996-7596 or FAX 313/996-7890.

REVIEWS COMPLETED	
CSO ACTION:	AP LV
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/	8-4-97
CSO INITIALS	DATE

Sincerely,

Sean Brennan
for Sean Brennan

SB:lk
t:\nda\20-720\064.doc

cc: Dr. David Woodward - Sankyo U.S.A. Corporation

APPEARS THIS WAY
ON ORIGINAL

July 8, 1997

SOS-005-005

PARKE-DAVIS

NDA 20-720/S-005
Ref. No. 63
Rezulin™ (troglitazone) Tablets

Sean Brennan, Ph.D.

Re: Chemistry, Manufacturing and
Controls Amendment to Supplement
(S-005): 300 mg Tablets Strength

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Sobel:

In response to a request by Dr. Xavier Ysern of your Division, attached are copies of the proposed container labels for the 300 mg Tablets in bottle of 60 and 120 count and blister packages. Dr. Ysern also requested information regarding the Environmental Assessment for this supplement.

all
8-JUL-1997
cmc
review
/S/
7/8/97

A waiver of the Environmental Assessment for the 300 mg Tablet is requested as a significant increase in usage is not expected. The Environmental Assessment in the original application and in the supplement (S-002) adding additional indications encompasses all tablet strengths for this product. The maximum approved daily dose of troglitazone is 600 mg. In order to provide a more convenient means to deliver this dose, 300 mg Tablet has been developed and added to the existing tablet strengths of 200 mg and 400 mg. The marketing forecasts used to estimate amounts of troglitazone released to the environment included all indications that would use Rezulin Tablets. The 300 mg Tablet is intended to replace the current strengths for those patients requiring a 600 mg dose.

Should you have any questions or comments regarding this supplement, please contact me at 313/997596 or FAX 313/996-7890.

Sincerely,

Match
/S/
7/16/97 for Sean Brennan
Phil Simonson

SB/rp t:\nda\20-720\070897-063

Attachment

REVIEWS COMPLETED
ACTION: LETTER N.A.I. MEMO
/S/ 8-1-97
CSO INITIALS DATE

Pharmaceutical
Research

PARKE-DAVIS

NDA NO. _____ REF. NO. _____
NDA SUPPL FOR _____

Sean Brennan, Ph.D.

June 17, 1997

NDA 20-720
Ref. No. 57
Rezulin™ (troglitazone) Tablets

Re: Special Supplement:
Changes Being Effected
New Tablet Strength

No. Pre-approval needed

po clinical problem /S/
300mg would be useful clinically /S/
TS/ 6/20/97
7/16/97

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Does not qualify as CBE, Pre approval needed /S/ 6/24/97

Dear Dr. Sobel:

Reference is made to NDA 20-720 for Rezulin™ (troglitazone) Tablets. The purpose of this supplement is to add a new tablet dosage strength of 300-mg.

The maximum approved daily dose of troglitazone is 600-mg. In order to provide a more convenient means to deliver this dose, a 300-mg tablet has been developed and added to the existing tablet strengths of 200-mg and 400-mg. The composition of the 300-mg tablet

In addition, the film coat used for the 300-mg tablet

Chemistry, manufacturing and control information for troglitazone 300-mg film-coated tablets is provided in the attachment.

The 300-mg tablet is a white, oval, film-coated tablet debossed with PD 357 on one side, and with 300 on the other side. Commercially, the 300-mg tablets will be packaged in _____, bottles of 60 and 120 tablets using the currently approved packaging components. In addition, the tablets will be made available in _____ blister packages for use as unit-dose packages and as physician samples. The same blister packaging components used for the currently approved strengths will be used for the 300-mg tablets.

CSE N-Tr: Sponsor called 6/24/97 1515 and informed that Harris does NOT qualify for CBE. OK with them. /S/

Solomon Sobel, M.D.
NDA 20-720
June 17, 1997
Page 2

Two lots of 300-mg tablets have been prepared manufacturing facility and have been packaged as indicated above. The lots will be placed on stability, and the studies will be performed according to the conditions recommended by the International Conference on Harmonization (ICH) of Regulatory Requirements. The results of these studies will be provided to the Food and Drug Administration in the Annual Report as permitted under 21 CFR 314.81 (b)(2)(iv), or as specified by the Agency.

Since the 300-mg tablet is bracketed by the approved strengths and the only change in the composition of the tablets is the deletion of color, no stability data has been provided at this time. Test results for both lots is provided in the attachment along with dissolution profiles on 12 units in the approved dissolution medium.

If you have any questions or comments regarding this submission, please contact me at 313/996-7596 or Phil Simonson at 313/996-5781 or FAX 313/996-7590.

Sincerely,

Sean Brennan

Sean Brennan

SB\ps\rm
t:\nda\20-720\061697-057

Attachments

cc: Ms. Regina Brown - Newark District Office
Ms. Diana Amador - San Juan District Office

APR 13 1997
FEDERAL

REVIEWS COMPLETED	
CSO ACTION: AP 8-4-97	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/	8-4-97
CSO INITIALS	DATE

APR 13 1997
FEDERAL



Food and Drug Administration
Rockville MD 20857

NDA 20-720/S-006

NOV 6 1997

PARKE-DAVIS RESEARCH AND DEVELOPMENT
DIVISION OF WARNER-LAMBERT COMPANY
2800 Plymouth Road
Ann Arbor, MI 48106-1047

Attention: Irwin G. Martin, Ph.D., Vice President, FDA Liaison, Worldwide Regulatory Affairs

Dear Dr. I. G. Martin:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: REZULIN (Troglitazone) Tablets

NDA Number: 20-720

Supplement Number: S-006

Date of Supplement: October 28, 1997

Date of Receipt: October 29, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 28, 1997, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,
ES

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-720/S-006

Page 2

cc:

Original NDA 20-720/S-006

HFD-510/Div. Files

HFD-510/CSO/M. Johnston

filename:

SUPPLEMENT ACKNOWLEDGEMENT

Pharmaceutical
Research

2800 Plymouth Road
Ann Arbor, MI
48105

Phone: (313) 996-7756
Facsimile: (313) 998-2856
E-Mail: martin@aa.wl.com

NDA SUPPLEMENT ORIGINAL

 **PARKE-DAVIS**
People Who Care

NDA NO. _____
NDA SUPPL FOR _____

J. Martin, Ph.D.
Vice President, FDA Liaison
Worldwide Regulatory Affairs

October 28, 1997

NDA 20-720
Ref. No. 69
Rezulin® (troglitazone) Tablets

Re: **Special Supplement -
Changes Being Effected**

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



*Noted
with related
issues are
acceptable
/S/
12-NEV-1997*

Dear Dr. Sobel:

Reference is made to our approved NDA for Rezulin® (troglitazone) Tablets, NDA 20-270. Additional reference is made to our teleconference with Dr. Robert Misbin of your Division on October 15, 1997, meeting background materials provided to _____ on October 21, 1997 (Serial No. 307), and our meeting on October 24, 1997, to discuss recent reports of hepatic dysfunction obtained from our spontaneous event reporting system.

Enclosed within is a Special Supplement - Changes Being Effected which includes a new WARNINGS section to describe these reports. Changes to upgrade or add ADVERSE EVENTS, PRECAUTIONS, or WARNINGS are permitted as a Special Supplement - Changes Being Effected pursuant to 21 CFR 314.70(c)(2)(i).

Attached are changes to the Rezulin labeling (Attachment 1). A description of these changes follow in Attachment 2. We have incorporated the Division's suggestions from our October 24 meeting and added information as agreed. We have further emphasized the first paragraph of the warning by adding bold, capitalized type.

*Noted
/S/
11/12/97*

Solomon Sobel, M.D.

NDA 20-720

October 28, 1997

Page 2

We have finalized the "Dear Doctor" letter to physicians and other healthcare professionals incorporating the Division's comments as well as those of DDMAC. A copy of the finalized text is included in Attachment 3. The printed version of the letter will be submitted to the NDA when available at the time of mailing. We anticipate sending the letter to approximately 300,000 physicians who have prescribed oral antidiabetic therapy in the last year, 70,000 pharmacists, and 9,000 diabetes educators. We hope to mail the letter on Friday, October 31, 1997. As physicians may begin receiving the letter on Monday, we ask that the agency provide the labeling on the MedWatch Home Page on Monday, November 3rd.

Given our mutual desire to provide the healthcare community with important information as quickly as possible, we will immediately disseminate the new labeling and commit to assemble an outside panel of experts to assist the agency and Parke-Davis in reviewing future reported serious hepatic events.

We will quickly revise our patient informational handouts to alert the patient to the signs and symptoms of hepatic dysfunction.

Please also note that all changes made to the Rezulin labeling will be made to the Prelay® (troglitazone, Sankyo U.S.A.) labeling. For this reason, Dr. Woodward from Sankyo U.S.A. attended our October 24 meeting.

Should you have any questions regarding this submission, please contact me at 313/996-7756 or FAX 313/998-3283.

Sincerely,

Mary G. Taylor for
Irwin G. Martin

IM\rm
t:\nda\20-720\102797-69

Attachments

Desk Copy: Dr. R. Misbin
Dr. A. Fleming

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Ok to implement
/S/
11/2/97



November 6, 1997

NDA 20-720
Ref. No. 70
Rezulin® (troglitazone) Tablets

Re: Sankyo NDA Reference Permission

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Sobel:

Reference is made to our approved application for Rezulin® (troglitazone) Tablets.

Permission is hereby granted to Sankyo U.S.A. Corporation to include by reference the complete contents of NDA 20-720 and Ref. No. 69 dated October 28, 1997.

If there are any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

Sincerely,

Mary E. Taylor, M.P.H.
Director
Worldwide Regulatory Affairs

Noted /S/ 12/4/97

APPEARS THIS WAY
ON ORIGINAL

MT\rm
t:\nda\20-720\110597-70

cc: Dr. David Woodward - Sankyo U.S.A. Corporation

*MC to please
/S/
12/4/97*

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
<i>/S/ 12-4-97</i>	
CSO INITIALS	DATE

*MSF
/S/
12/4/97*

PARKE-DAVIS

November 7, 1997

NDA 20-720
Ref. No. 71
Rezulin® (troglitazone) Tablets

Re: Final Printed Letter

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Sobel:

Reference is made to our supplement of October 28, 1997 (Ref. No. 69) regarding a labeling change and letter to healthcare professionals.

As mentioned in the letter, attached is a final printed copy of the letter and envelope that went to healthcare professionals.

Also, as requested, a copy of the letter and envelope is being sent to Diane Kennedy, MedWatch Program, FDA.

If there are any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> FTFR <input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/ 12-4-97
CSO INITIALS DATE

Sincerely,

Mary E. Taylor

Mary E. Taylor, M.P.H.
Director
Worldwide Regulatory Affairs

MT\rm
t:\nda\20-720\110597-71

Attachment

cc: Ms. Diane Kennedy, HF-2, Room 957, Parklawn

Noted /S/ 12/4/97

Noted /S/ 12/4/97

MAI /S/ 11/24/97



November 26, 1997

NDA 20-720
Rezulin® (troglitazone) Tablets

Re: Final Printed Labeling - Desk Copies

Michael Johnston, R.Ph.
Regulatory Management Officer
Division of Metabolic and Endocrine
- Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers
Rockville, Maryland 20857



Dear Mr. Johnston:

Reference is made to our approved NDA 20-720 for Rezulin® (troglitazone) Tablets. Reference is also made to our October 28, 1997, "Special Supplement - Changes Being Effected" (S-006), which included a new WARNINGS section and changes to the ADVERSE REACTIONS, PRECAUTIONS and WARNINGS sections to include reports of hepatic dysfunction.

Included herein are ten desk copies of the revised Rezulin package insert per your November 18, 1997, E-mail request to Mary Taylor. The specification number of this package insert is 0352G201 and the revision date is October 1997.

Should you have any questions or require additional information, please contact me at 201/540-3113 or FAX 201/540-5972.

REVIEWS COMPLETED	
CSO ACTION: <i>A.P.L.</i>	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
<i>/S/</i>	<i>12-3-97</i>
CSO INITIALS	DATE

Sincerely,

James A. Parker, Jr.
Director
Advertising and Labeling
Worldwide Regulatory Affairs

*Supplement A binds approved
- extra labeling copies only
/S/
12-3-97*

ORIGINAL
NDA SUPPL AMENDMENT
SUPPL NEW CORRES



J. Martin, Ph.D.
Vice President, FDA Liaison
Worldwide Regulatory Affairs

December 2, 1997

NDA 20-720
Ref. No. 72
Rezulin® (troglitazone) Tablets

Noted
/S/
12/11/97

Re: Draft Labeling

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Sobel:

Reference is made to our approved NDA for Rezulin® (troglitazone) Tablets, NDA 20-720. Additional reference is made to our labeling supplement, S-006, submitted as a Change Being Effected on October 28, 1997. Further reference is made to our discussions with the agency during the past week concerning additional changes to the approved labeling relating to reports of hepatic dysfunction obtained via the spontaneous reporting system.

As agreed, we have provided as Attachment 1 additional proposed changes to the labeling. Upon agreement, these changes will be submitted as a Change Being Effected Labeling Supplement. The Clinical Studies, Monotherapy subsection of CLINICAL PHARMACOLOGY has been revised to include additional data from clinical studies 991-031 and 991-032. The report from study 991-032, RR 720-03608, was submitted to this NDA on February 3, 1997. Page 26 from this report, which contains the results for the relevant analysis, is provided in Attachment 2. Additionally, results of a similar analysis from study 991-031 is provided in this attachment. The report for this study, submitted to the NDA on July 31, 1996, did not contain this analysis.

Noted
/S/
11-DEC-1997

The proposed changes further minimize the risk to patients on Rezulin by increasing frequency of liver function tests. Therefore, the benefit to risk ratio for all Rezulin indications, including monotherapy, remains favorable.

Note: This labeling already superseded by new labeling

/S/

/S/

Solomon Sobel, M.D.
NDA 20-720
Page 2
December 2, 1997

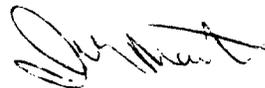
Upon finalization of the revised labeling, Parke-Davis will provide approximately 500,000 US physicians, pharmacists and diabetes educators with the new labeling. On December 1, we alerted these health care providers (495,259 physicians, 62,570 pharmacists, 9,039 diabetes educators) to the pending labeling change via fax or "Statgram" (Attachment 3). The direct fax or mailing to these professionals, the follow-up labeling, as well as the press attention which these changes have received, will assure to the greatest extent possible that prescribing physicians are aware of the changes. The follow-up labeling will be mailed with standard Parke-Davis Medical Affairs letterhead.

As we are both anxious to provide the revised labeling to prescribing physicians, we ask for your expeditious review of the attachment.

Please note that we are submitting for review to DDMAC a direct-to-consumer advertisement which concerns the change in LFT monitoring. As we hope to publish this advertisement in a few days, we particularly need your rapid approval on the changes to the WARNINGS and ADVERSE REACTIONS section of the labeling so we can change the "Brief Summary" which will accompany the ad.

Should you have any questions regarding this submission, please contact me at 313/996-7756 or FAX 313/998-3283.

Sincerely,



Irwin G. Martin

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/	12-12-97
CSO INITIALS	DATE

IM\rm
t:\nda\20-720\120297-72

Attachments

Desk Copy: M. Johnston (via FAX)

NDA 20-720/S-007

—

CSO REVIEW OF REVISED PACKAGE INSERT

NDA 20-720/S-006

Rezulin (Troglitazone) 200 mg, 300 mg, and 400 mg tablets

Reviewed: December , 1997 by Michael F. Johnston, Project Manager

Labeling Pieces Reviewed: from submission dated October 28, 1997)

New Draft Package Insert (Serial #0352G202V3/Dec,1997), compared to previous approved fpl package insert (Serial #0352G201/Oct,1997) submitted on September 18, 1997 and to the draft package insert approved in labeling negotiations on December 4 - 10, 1997, 1997 in response to reported hepatic adverse events.

Changes Noted:

A. Creates New Black Box Warning at the beginning of the label. See Attachment #1 for text. This box will be moved on the fpl from the WARNINGS section to the beginning of the label.

B. **CLINICAL PHARMACOLOGY/Special Populations:** New wording to reflect hepatic warning. See Attachment (1) for wording.

C. **CLINICAL PHARMACOLOGY/Monotherapy:** Adds wording to reflect response rate for Rezulin monotherapy. See Attachment (1) for wording.

D. **INDICATIONS AND USAGE:** Adds "See DOSAGE AND ADMINISTRATION" to end of second sentence.

E. **PRECAUTIONS/Use in Patients with Heart Failure:** Moves this section to the PRECAUTIONS/General subsection.

F. **ADVERSE REACTIONS:** Modifies wording to enhance hepatotoxicity symptoms information. See Attachment #1 for wording.

G. **ADVERSE REACTIONS/Postintroduction Reports:** Modifies wording to clarify which adverse events (Included CHF related events) have not had causal relationship to Rezulin determined. See Attachment #1 for wording.

NDA 20-720/S-007

H. DOSAGE AND ADMINISTRATION/Monotherapy: Adds reference to CLINICAL PHARMACOLOGY/Clinical Studies/Monotherapy section. Also adds phrase "Rezulin should be discontinued and" to the text. See attachment #1 for wording.

I. DOSAGE AND ADMINISTRATION/Patients with Hepatic Impairment: Wording added (See Attachment #1) to clarify that Rezulin should NOT be started in patients with evidence of liver disease.

ATTACHMENT #1: Annotated Rezulin Labeling Dated 12/12/97

NDA 20-720/S-007

NDA 20-720/S-007

Review of Draft Printed Labeling with Hepatic Adverse Event Changes from S-007.
Please note that the fpl will contain the black box warning at the beginning of the label
(instead of the WARNINGS section).

REVIEWERS NOTE: Please sign below (in addition to routing slip)

/S/ 12/15/97
Medical Officer/date

/S/ 12/30/97
Medical Tm Ldr signature/date

/S/ 30-DEC-1997
Chemist/date

/S/
Chemistry Tm Ldr Sign/Date

/S/ 12/22/97
Pharmacologist/date

/S/ 12/30/97
Pharmacology Tm Ldr Sign/Date

/S/
Michael F. Johnston, R.Ph.
Project Manager/date

/S/
SCSO/date 12/29

cc: Original NDA File: NDA 20-720
HFD-510: MJohnston

Q

Page(s) Redacted

DRAFTING LABELING



Food and Drug Administration
Rockville MD 20857

NDA 20-720/S-007

Parke-Davis Research and Development
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48106-1047

Attention: Irwin G. Martin, Ph.D., Vice President, FDA Liaison, Worldwide Regulatory Affairs

Dear Dr. I. G. Martin:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: REZULIN (troglitzone) Tablets

NDA Number: 20-720

Supplement Number: S-007

Date of Supplement: December 5, 1997

Date of Receipt: December 8, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on January 4, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-720/S-007

Page 2

cc:

Original NDA 20-720/S-007

HFD-510/Div. Files

HFD-510/CSO/M. Johnston

filename:

SUPPLEMENT ACKNOWLEDGEMENT

Pharmaceutical
Research

2800 Plymouth Road
Ann Arbor, MI
48105

NDA SUPPLEMENT
NDA 20-720-736
Facsimile: (313) 998-2856
E-Mail: martin@aa.wi.com

NDA NO. _____ REF. NO. _____

NDA SUPPL FOR _____

PARKE-DAVIS
People Who Care

J. Martin, Ph.D.

President, USA Division
Worldwide Regulatory Affairs

December 5, 1997

NDA 20-720
Ref. No. 73
Rezulin® (troglitazone) Tablets

Re: Supplement:
Expedited Review Requested

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Sobel:

Reference is made to our approved NDA for Rezulin® (troglitazone) Tablets, NDA 20-720. Additional reference is made to our labeling submission of December 2, 1997, Ref. No. 72, our meeting of December 3, 1997, facsimile to Mr. M. Johnston of December 4 containing updated labeling and to my telephone conversation with Dr. A. Fleming of December 4. These labeling changes relate to reports of hepatic dysfunction.

Enclosed within is a Supplement which includes changes to upgrade and add information to the CLINICAL PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the labeling. Four copies of draft labeling in the format of final printed labeling is provided.

As we are both anxious to provide the revised labeling to prescribing physicians, and as this does not qualify as a Changes Being Effected Supplement under 21 CFR 314.70 (c)(2)(i), we ask for your expeditious review of the attachment.

Please note that all changes made to the Rezulin labeling will also be made to the Prelay® (troglitazone, Sankyo U.S.A.) labeling.

updated /S/

Solomon Sobel, M.D.
NDA 20-720
Page 2
December 5, 1997

Permission is hereby granted to Sankyo U.S.A. Corporation to include by reference the complete contents of NDA 20-720 and this submission.

Should you have any questions regarding this submission, please contact me at 313/996-7756 or FAX 313/998-3283.

Sincerely,



Irwin G. Martin

IM\rm
t:\nda\20-720\120497-73

Attachment

Desk Copy: M. Johnston

REVIEWS COMPLETED	
CSO ACTION: AP 12-11-97	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/	12-30-97
CSO INITIALS	DATE

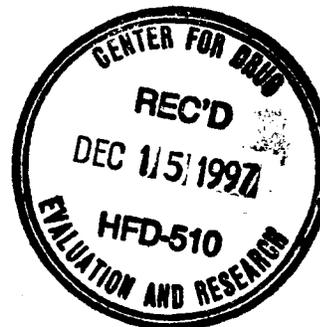


December 12, 1997

NDA 20-720
Ref. No. 75
Rezulin® (troglitazone) Tablets

Re: Amendment to December 5, 1997
Supplement (S-007)

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Sobel:

Reference is made to our approved NDA for Rezulin® (troglitazone) Tablets, NDA 20-720 and to our labeling supplement submitted December 5, 1997 (S-007). Reference is also made to conversations the week of December 8, 1997 regarding the labeling and specifically a teleconference with Drs. Bilstad, Sobel, Fleming, and Misbin on December 11, 1997.

*Noted
/S/
12/22/97*

Enclosed within is an amendment to our supplement upgrading and adding information to the Warnings and Adverse Reactions sections of the labeling. Four copies of draft labeling in the format of final printed labeling is provided.

Also attached is a two column version of the labeling indicating the location of the agreed upon changes.

Please note that all changes made to the Rezulin labeling will also be made to the Prelay® (troglitazone, Sankyo U.S.A.) labeling. Permission is hereby granted to Sankyo U.S.A. Corporation to include by reference the complete contents of NDA 20-720 and this submission.

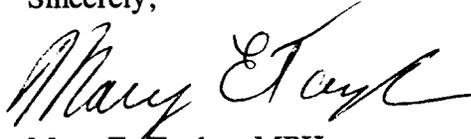
*Noted
/S/
12/22/97*

Solomon Sobel, M.D.
NDA 20-720
December 12, 1997
Page 2

If you have any questions, please contact me at 313/996-5000 or FAX 313/998-3283.

REVIEWS COMPLETED	
CSO ACTION	AP 2x-
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/	12-15-97
CSO INITIALS	DATE

Sincerely,



Mary E. Taylor, MPH
Director
Worldwide Regulatory Affairs

MT\rm
t:\nda\20-720\121297-75

Attachments

Change in order & void
to be made in the next printing -
in the post-marketing section need
to be made ~~to be~~ please inform
Sparrow

/S/

12/18/97

NOV 18 1997

NDA 20-720/S-006

CSO REVIEW OF REVISED PACKAGE INSERT

NDA 20-720/S-006

Rezulin (Troglitazone) 200 mg, 300 mg, and 400 mg tablets

Reviewed: November 13, 1997 by Michael F. Johnston, Project Manager

Labeling Pieces Reviewed: from submission dated October 28, 1997)

New FPL Package Insert (Serial #0352G201/Oct,1997), compared to previous approved fpl package insert (Serial #0352G200/Aug,1997/submitted on September 18, 1997 and to the draft package insert approved in labeling negotiations on October 27, 1997 in response to reported hepatic adverse events.

Changes Noted:

A. **WARNINGS:** New Bolded Section to reflect recent cases of hepatic adverse events: See Attachment #1 for Wording.

B. **PRECAUTIONS/General:** Section modified to move paragraph on hepatic precautions from PRECAUTIONS/General section to **WARNINGS** section (see "A" above)

C. **PRECAUTIONS/Information for the Patients Section:** Adds new paragraph related to hepatic adverse event symptoms. See Attachment #1 for wording.

D. **ADVERSE REACTIONS/Serum Transaminase Levels:** At beginning of paragraph, adds sentence "During all clinical studies in North America, a total of 48 of 2510 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal."

At the end of paragraph, changes "(see PRECAUTIONS, General, Hepatic)" to "(see WARNINGS)."

F. **ADVERSE REACTIONS/Postintroduction Reports:** Adds this new section to end of section with the following wording:

Adverse Events associated with Rezulin that have been reported since market introduction, that are not listed above, and for which casual relationship to drug has not been established

NDA 20-720/S-006

include the following: jaundice, hepatitis, liver transplant, death. Also see WARNINGS.

After a thorough review of the label, these are the only changes noted in the new fpl.

NDA 20-720/S-006

NDA 20-720/S-006

Review of Final Printed Labeling with Hepatic Adverse Event Changes from S-006

REVIEWERS NOTE: Please sign below (in addition to routing slip)

/S/ 11/17/97

Medical Officer/date

/S/ 11/15/97

Medical Tm Ldr signature/date

/S/

Chemist/date

Chemistry Tm Ldr Sign/Date

11/17/97

/S/ 11/13/97

Pharmacologist/date

/S/

Pharmacology Tm Ldr Sign/Date

11/17/97

/S/ Michael F. Johnston, R.Ph.
Project Manager/date

/S/

SCSO/date

11/18/97

cc: Original NDA File: NDA 20-720
HFD-510: MJohnston
HFD-510 / DM Files