Webby

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-720/S-012

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48105-1047

NOV 24 1998

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

Dear Ms. Taylor

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Rezulin® (troglitazone) Tablets
NDA Number:	20-720
Supplement Number:	S-012
Date of Supplement:	November 18, 1998
Date of Receipt:	November 19, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on January 18, 1999, 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,

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

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

June 11, 1999

NDA 20-720
Ref. No. 106
Rezulin® (troglitazone) Tablets

Re: Revised Package Insert

Solomon Sobel, M.D.
Director
Division of Metabolism 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:

On behalf and as agent for Parke Davis Pharmaceuticals, Limited, reference is made to our pending Supplement S-012 for triple therapy with metformin and sulfonylureas.

Reference is also made to our teleconference on June 10, 1999 with the Division of Metabolism and Endocrine Drug Products and Drug Marketing and Advertising.

Attached is the revised package insert that is inclusive of all discussions and agreements with members of the Division.

Two mistakes were corrected in the section Combination With Sulfonylurea and Metformin. The –42 nmol/L was corrected to –43 mg/dL and the phrase "a 10% increase reduction in fasting C-peptide" was corrected to remove the word reduction.

If you have any questions or require additional information, please contact me at 734/622-5000 or via FAX at 734/622-3283.

Sincerely,

Mary E. Taylor, MPH
Director
Worldwide Regulatory Affairs

MT\rm
06-11-1999\RN-106\20-720\CI-0991\Letter

Attachment

Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-5210
Facsimile: (734) 622-5070

PARKE-DAVIS

May 4, 1999

NDA 20-720/S-012
Ref. No. 104
Rezulin® (troglitazone) Tablets

Re: Labeling

William M. Merino, Ph.D.
Senior Vice President
Worldwide Regulatory Affairs

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 pending Supplement S-012 for combination therapy with metformin and sulfonylureas. Reference is also made to your labeling comments faxed to Parke-Davis on April 21, 1999 and our meeting to discuss labeling scheduled for May 12 at 4:00 PM.

Based on your comments as well as those of the Endocrinologic and Metabolic Drugs Advisory Committee, we have revised the Indication and Dosage and Administration sections of the package insert (Attachment 1).

The patient information leaflet has also been revised as requested at our March 19 meeting with the exception of Answer 4. A revised patient information leaflet containing our proposed Answer 4 is attached (Attachment 2). One of the major pharmacy information groups currently does not include monitoring information in its database. This is the patient information distributed by retail pharmacists to patients. We will continue our efforts to have the patient information revised but will be providing the patient information leaflet to the pharmacies for direct distribution to the patient.

Parke-Davis would like to make you aware of some of the new initiatives that are being planned or underway.

1. Epidemiological studies evaluating a broad spectrum of adverse events among patients on oral antidiabetic agents.

2. Prospective study evaluating the frequency of liver function monitoring following Rezulin use.

3. Validation study of the United HealthCare database using physician chart audits.

4. Prospective study monitoring the occurrence of liver transplants in patients with diabetes.

5. The Rezulin Rezults program was initiated in March. Initial feedback from physicians and patients has been positive. The program will eventually involve over 65,000 physicians. The program offers:
   - monthly reminders for patients to schedule recommended liver enzyme tests
   - monthly tips and educational materials
   - at home HbA_{1c} test kits

6. The cardiac study 991-107 currently has 45 patients enrolled at 19 sites. We expect completion of this study by the end of the year.

7. The Rezulin pregnancy registry, an observational study evaluating the rates of major malformations among women who become pregnant while on troglitazone, was initiated in July 1998. Enrollment is continuing.

We have had numerous questions regarding the United HealthCare study discussed by Dr. Graham at the March 26 Advisory Committee meeting. We have asked Dr. Graham to provide the supporting documentation. This information would help us in designing future studies.

Should you have any questions or comments regarding this submission, please contact me at 734/622-5210 or via FAX at 734/622-5070.

Sincerely,

Mary Taylor for

William Merino

WM\mt\rm
05-04-1999\RN-104\20-720\CI-0991

Attachments

Desk Copy: J. Weber (HFD-510, 5 copies)
J. Bilstad (HFD-102)
J. Jenkins (HFD-102)

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

March 31, 1999

NDA 20-720/S-012
Ref. No. 102
Rezulin® (troglitazone) Tablets

Re: 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

DESK COPY

Dear Dr. Sobel:

Reference is made to our pending Supplement S-012 for combination therapy with metformin and sulfonylureas. Reference is also made to labeling comments faxed to Parke-Davis on February 16, 1999.

The proposed labeling has been revised based on these comments as well as those from the March 26, 1999 Endocrinologic and Metabolic Drugs Advisory Committee meeting.

We propose the following:

1) Box Warning - Rezulin therapy should not be initiated if the patient has a history of liver disease or exhibits clinical evidence of active liver disease, cirrhosis, hepatitis history of alcohol abuse, or increased serum transaminase levels (ALT >1.5 times the upper limit of normal).

2) The above statement will be added to the Contraindications section.

3) The monotherapy trial will be shortened to 1 month and limited to those patients with FSG levels less than 200 mg/dL

I have attached a document that describes the original supplement labeling proposal, the comments from FDA and comments from Parke-Davis. Attachment 2 contains the revised labeling highlighted for ease of review.

Monotherapy – in naive patients only?
– who have failed SU, therapy?

Should you have any questions or comments regarding this submission, please contact me at 734/622-5000 or via FAX at 734/622-3283.

Sincerely,

Mary E. Taylor, MPH
Director
Worldwide Regulatory Affairs

MT\dp
03-31-1999\RN-102\20-720\CI-0991\Letter

Attachments

Desk Copies: J. Weber (HFD-510) 5 Copies

APPEARS THIS WAY
ON ORIGINAL

Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-7000

PARKE-DAVIS

SE1-012 BM

NDA SUPP AMEND

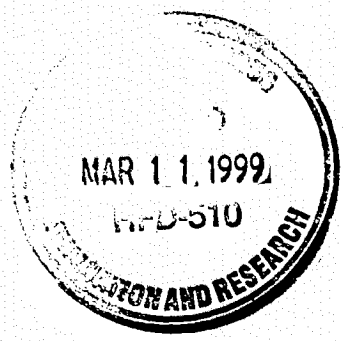
ORIGINAL

March 10, 1999

NDA 20-720
Ref. No. 100
Rezulin® (troglitazone) Tablets

Re: Response to Request for Information

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 pending supplement S-012 for Rezulin® (troglitazone) Tablets. Please find attached the following corrections to Research Report No. 720-04107 entitled, "A Double-Blind, Randomized Study of Troglitazone (CI-991) Versus Placebo in Type 2 Diabetes Patients With Compromised Glycemic Control on a Combination Therapy of Sulfonylurea and Metformin (Protocol 991-105)," submitted with our supplemental sNDA on November 18, 1998 (Reference No. 90).

noted
/S/
3/12/99

Please find attached the following corrected information:

- Pages 49 and 50
- Appendix C.20

This research report can be found in the sNDA Volumes 2-4. Pages 49 and 50, and Pages 29 and 30 from Appendix C.20 were faxed to Dr. Lee Ping Pian of the FDA on March 10, 1999.

/S/
3/12/99

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

If you have any additional questions, please contact me at 734/622-5000 or via FAX at 734/622-3283.

Sincerely,

Mary E. Taylor, MPH
Director
Worldwide Regulatory Affairs

MT\dp
03-10-1999\RN-100\20-720\CI-0991\Letter
Attachments

APPEARS THIS WAY
ON ORIGINAL

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

ORIGINAL

Study 991-105

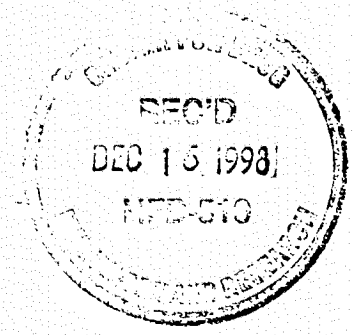
December 15, 1998

NDA SUPP AMEND
SE1-012 EVC

NDA 20-720
Ref. No. 92
Rezulin® (troglitazone) Tablets

Re: Response to Request for Information

Solomon Sobel, M.D.
Director
Division of Metabolism 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 pending supplement S-012 for troglitazone and to requests on December 10 and December 11, 1998, by Dr. R. Misbin of your Division for additional information.

Please find attached the following information:

1) Study 991-105 Analysis of FS6 and $HbA1_c$ by Metformin dose.
2) Study 991-075 Individual Patient Data
   a) Fasting $HbA1_c$
   b) Fasting Blood Glucose
   c) Glucose Disposal Rate
   d) Lipid Parameters
   e) Meal Tolerance Test
   f) Weight and BMI

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 12/17/98
CSO INITIALS DATE

CONCUR NAI

Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-7000

PARKE-DAVIS

ORIGINAL

December 8, 1998

NDA 20-720
Ref. No. 91
Rezulin® (troglitazone) Tablets

NDA SUPP AMEND
SE1-012
BM

Re: Response to Request for Information

CENTER FOR DRUG
REC'D
DEC 09 1998
EVALUATION & RESEARCH

Solomon Sobel, M.D.
Director
Division of Metabolism 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

REVIEWS COMPLETED
CSO ACTION:
☑ LETTER ☐ N.A. ☐ MEMO
/S/ 1/6/99
CSO INITIALS DATE

Dear Dr. Sobel:

Reference is made to our pending supplement S-012 submitted November 18, 1998 and to a request from Dr. R. Misbin of your Division on December 2, 1998 for the following attached information:

1) Study 991-075 individual patient information for efficacy parameters.
2) Study 991-105 distribution of metformin daily dose. We have further committed to analyze the efficacy parameters at greater than or less than 2 grams of metformin per day. This analysis will be forthcoming.
3) Running text version of the proposed labeling.
4) Copy of the letter to the editor of NEJM entitled "Hepatic Dysfunction Associated with Troglitazone".

/S/ 1/6/99

Also requested was an update on our ongoing study cardiac safety study 991-107. We currently have 43 patients randomized; 9 patients have completed and an additional 12 patients have completed 5 months of therapy. No patients have withdrawn due to adverse events due to fluid expansion or decompensation of CHF. We have increased the number of sites participating in the study from 7 to 21.

/S/ 1/6/99

991-075, HbA1c Listing
991-075, FPG Listing
991-075, MTT Listing
991-075, Clamp Listing
991-105, metformin

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

ORIGINAL

NDA NO 20720 REF NO. 012

November 18, 1998 NDA SUPPL FOR SE1

NDA 20-720
Ref. No. 90
Rezulin® (troglitazone) Tablets

Re: Supplemental SNDA

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:

Pursuant to 21 CFR 314.70, enclosed is a supplement to the approved New Drug Application 20-720 for Rezulin® (troglitazone) Tablets. This supplement seeks to expand and modify the approved labeling to include Rezulin as combination therapy with metformin or with metformin and sulfonylureas in patients with type 2 diabetes.

As required under the FDA Modernization Act of 1997 a check for [redacted] has been sent to the Food and Drug Administration in care of the Mellon Bank, Philadelphia, Pennsylvania on November 9, 1998. The User fee Cover Sheet (Item 18 follows the Form 356h) [redacted]

Please refer to the attached Form 356h and the SNDA Index which detail the complete contents of this supplemental NDA.

Marketing Exclusivity Information and the Generic Drug Enforcement Act Certification are in Item 13, contained in Volume 1 of this SNDA.

This SNDA provides the results of two clinical studies with Rezulin in combination with metformin or metformin and sulfonylurea. A 24-week, uncontrolled, randomized, single-blind study comparing troglitazone and metformin as monotherapy (12 weeks) and as combination therapy (for an additional 12 weeks) was conducted in patients with NIDDM (N = 29) under IND [redacted] Troglitazone and metformin were equally effective in lowering fasting plasma glucose and postprandial glucose as monotherapy.

When therapy with these 2 drugs was combined, FSG decreased further, with a mean fall of an additional 41 mg/dL or 18% ($p = 0.001$) between month 3 and month 6. Compared to baseline values, the mean decrease in FSG in all subjects over the 6 month treatment period was 98 mg/dL, or 35% ($p = 0.001$). HbA_{1c} decreased during the 3 months of combination therapy, with a mean absolute fall of 1.2% ($p < 0.001$) from the subject's baseline on former anti-diabetic therapy.

In a separate 24-week double blind randomized study in patients with type 2 diabetes (N=196) who have failed to achieve glycemic control with the combination of a sulfonylurea and metformin either Rezulin or placebo were added. Patients randomized to receive a sulfonylurea with metformin and 400 mg of troglitazone, showed mean decreases in FSG and HbA_{1c} (-42nm/L and –1.3%, respectively). Similarly, there was a 9% reduction in endogenous insulin, a 10% increase in fasting C-peptide, and a 9% increase in HDL Forty-three percent of subjects receiving the combination of sulfonylurea, metformin, and troglitazone achieved adequate glycemic control of a less than 8% HbA_{1c} ($p<0.001$) while only 6% of patients achieved control with the sulfonylurea and metformin, and placebo combination.

Metformin and troglitazone share no pharmacokinetic characteristics that would suggest the potential for a pharmacokinetic interaction.[1] Metformin is eliminated almost entirely (79% to 100%) by renal excretion, with net tubular secretion, whereas troglitazone is eliminated primarily by metabolism, with no unchanged drug found in urine and most of the dose excreted in feces. Also, metformin is not bound to plasma proteins, whereas troglitazone is highly (>99%) protein bound. Moreover, there is substantial clinical experience with coadministration of metformin and troglitazone demonstrating that the combination is well tolerated and has enhanced efficacy.[2] In light of this body of information, we believe that a pharmacokinetic drug-drug interaction study of troglitazone and metformin is not warranted.

Additional research reports and published literature are also provided to support changes in the CLINICAL PHARMACOLOGY section of the labeling. These studies include a monotherapy comparative trial with metformin, a study on the effect of Rezulin on body composition, and two publications each on beta cell function and lipids. The safety data reported in all of the studies in this SNDA are consistent with the current approved labeling, therefore, that section of the labeling has not been updated.

If there are any questions or comments regarding this submission, please contact me at 734/622-5000 or FAX 734/622-3283.

Sincerely,

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

MT\rm
t:\nda\20-720\111898-90

Attachments

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

DATE

CSO INITIALS