CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020720, S12, S14

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CSO(weber)

APR 29 1999

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

sNDA:	**20-720 SE1-012**
Type of Submission:	**Supplement New Indication – Combination Therapy**
Generic Name:	**troglitazone**
Brand Name:	**Rezulin® Tablets**
Sponsor:	**Parke-Davis Ann Arbor, MI**
Submission Date:	**November 18, 1998**
Reviewer	**Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D**

Synopsis

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.

The sponsor states that "a pharmacokinetic drug-drug interaction study of troglitazone and metformin is not warranted", and presents the following argument:

> "Metformin and troglitazone share no pharmacokinetic characteristics that would suggest the potential for a pharmacokinetic interaction. 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 the urine and most of the dose excreted in the 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. In light of this information, we believe that a pharmacokinetic drug-drug interaction study of troglitazone and metformin is not warranted."

Conclusion

I agree with the essence of the sponsor's argument and the sponsor's conclusion.

Labeling Comments

There are no labeling changes that require comments by The Office of Clinical Pharmacology and Biopharmaceutics.

Draft labeling is attached.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II has reviewed sNDA 20-720 SE1-012 submitted 18 November 1998 and finds it acceptable.

Signatures

/S/

4/29/99

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

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

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

Code: AP

4/29/99

APPEARS THIS WAY
ON ORIGINAL