CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-202

PHARMACOLOGY REVIEW(S)

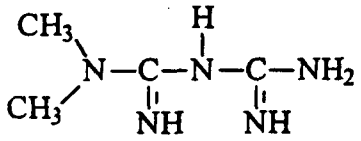
REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS:

Reviewer Name: Ronald W. Steigerwalt, Ph.D. Supervisory Pharmacologist
Division Name: Division of Metabolic and Endocrine Drug Products (DMEDP)
HFD#510
Review Completion Date: July 12, 2000
Review number: 1

IND/NDA NUMBER: NDA 21-202
Serial number/date/type of submission: N000 November 11, 1999
Information to sponsor: Yes ( ) No (X)
Sponsor (or agent): Bristol Meyers Squib Co.

DRUG
Generic Name: Metformin HCl
Trade Name: Glucophage XR
Chemical Name:N,N-dimethylimidocarbonimidic diamide HCl
Molecular Formula/ Molecular Weight: MW 165.63 $C_4H_{11}N_5 \cdot HCl$
Structure:



•HCl

Relevant INDs/NDAs/DMFs: Approved NDA ——

Drug Class: oral antihyperglycemic (non-sulfonylurea)

Indication: Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes.

Clinical formulation: 500, 850 or 1000 mg metformin hydrochloride with povidone and magnesium stearate as excipients. Coating contains hydroxypropyl methylcellulose and polyethylene glycol. Maximum Recommended Human Dose = 2550 mg/day.

Route of administration: oral

Previous clinical experience: Immediate release approved.

Disclaimer – use of sponsor's material: No sponsor materials are reproduced in this document.

INTRODUCTION AND DRUG HISTORY: The immediate release formulation of metformin is an approved product. There has been extensive clinical experience and the toxicities are well-characterized clinically. This NDA provides for an extended release formulation, which results in essentially the same daily exposure to the drug product. No preclinical studies were submitted in support of this NDA.

Studies reviewed within this submission: No preclinical studies were submitted. Preclinical sections of the label were reviewed.

Studies not reviewed within this submission: N/A

OVERALL SUMMARY AND EVALUATION:

Introduction: The immediate release formulation of metformin is an approved product. There has been extensive clinical experience and the toxicities are well-characterized clinically. This NDA provides for an extended release formulation, which results in essentially the same daily exposure to the drug product. No preclinical studies were submitted in support of this NDA. The overall daily exposure remains similar to the approved immediate release product. Formulation is unremarkable in terms of potential toxicities. The pharmacology review consisted of examination of the preclinical sections of the label to ensure accuracy. The preclinical sections have not been altered from those in the approved product. Therefore, pharmacology has no further comments and recommends approval of this NDA.

Conclusions: Pharmacology recommends approval of NDA 21-202.

COMMUNICATION REVIEW:
Labeling Review (NDA): Preclinical sections of label are unchanged from immediate release product. Daily exposure remains the same as immediate release, so no changes to these sections are necessary. Carcinogenicity and pregnancy category sections are adequate.

RECOMMENDATIONS:

Internal comments: Recommend approval from pharmacology standpoint. No label changes made to preclinical sections and none are needed.
External Recommendations (to sponsor): none

Reviewer signature/team leader signature [Concurrence/Non-concurrence]

/S/

Ronald W. Steigerwalt, Ph.D.
Supervisory Pharmacologist, DMEDP
7/14/00

cc: IND Arch
HFD510
HFD510/Steigerwalt/Weber
Review Code: AP
Filename 21202.000.doc