CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-178

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: labeling, combination product

Reviewer Name: Ronald W. Steigerwalt, Ph.D. Supervisory Pharmacologist
Division Name: Division of Metabolic and Endocrine Drug Products (DMEDP)
HFD#510
Review Completion Date: June 8, 2000
Review number: 1

IND/NDA NUMBER: NDA 21-178
Serial number/date/type of submission: N/000 September 30, 1999
Information to sponsor: **Yes (X)** No ( ) (labeling)
Sponsor (or agent): Bristol Myers Squibb

DRUG
Generic Name: Metformin/Glyburide fixed combination 500/5 mg, 500/2.5 mg and 250/1.25 mg

Relevant INDs/NDAs/DMFs: Approved NDA's 20-357 (glucophage, metformin HCl); 20-174 (Glyburide).

Drug Class: sulfonylurea (glyburide); insulin sensitizer (non-PPAR acting-metformin)

Indication: treatment of type 2 diabetes

Clinical formulation:
250/1.25; 500/2.5 or 500/5 mg metformin and glyburide tablets contain the following inactive ingredients:
microcrystalline cellulose, povidone, croscarmellose sodium and magnesium stearate

Route of administration: oral

Proposed clinical protocol or Use: Use in type 2 diabetics. Maximum recommended human dose is 2000/20 mg/day of metformin/glyburide components.

Previous clinical experience: Individual drugs approved for treatment of type 2 diabetes. Combination treatment of the two drugs is commonly used clinically.

Disclaimer -- use of sponsor's material: none

INTRODUCTION AND DRUG HISTORY: The sponsor initiated contact with the agency regarding development on October 17, 1996. At that time, there was no clear policy on preclinical testing of fixed combination drugs. It was determined that since there was extensive use of the combined products (as separate entities) in humans that no preclinical studies were necessary provided that the chemistry showed that there was no interaction of the drugs when combined and stored in a single tablet. The sponsor has provided no new preclinical data and cites the previously approved NDA's for support for preclinical sections of the label. This reviewer has attempted to clarify and update the proposed labeling for the fixed combination product. Note that some current labeling

conventions were not possible because the necessary data were not available from reviews of the approved products.

Studies reviewed within this submission: no preclinical studies were submitted. Preclinical sections of the label are reviewed and revised as possible with available data.

Studies not reviewed within this submission: none

PHARMACOLOGY RECOMMENDATIONS FOR PRECLINICAL SECTIONS OF THE LABEL

Carcinogenisis, Mutagenesis, Impairment of Fertility.

No ——— **animal** studies have been conducted with **the combined products in** ——— **The following data are based on findings in studies performed with the individual products.**

Metformin Hydrochloride
Long-term carcinogenicity studies ——— **were** performed **with metformin alone** in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately — **four** times the maximum recommended human daily dose **of 2000 mg of the metformin component of** ——— **based** on a body surface area **comparisons** — No evidence of carcinogenicity with metformin **alone** was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin **alone** in male rats. **There was,** however, an increased incidence of benign stromal uterine polyps ——— in female rats treated with 900 mg/kg/day **of metformin alone**.

There was no evidence of a mutagenic potential of metformin **alone** ——— in the **following *in vitro* tests:** Ames test *(S. typhimurium)*, gene mutation test (mouse lymphoma cells); **or** chromosomal aberrations test (human lymphocytes)., ——— **Results in the *in vivo* mouse micronucleus test were also negative.**

Fertility of male or female rats was unaffected by metformin **alone when administered** ——— at doses as high as 600 mg/kg/day — **which is** approximately — **three** times the maximum recommended human daily dose **of the metformin component of** ——— **based on body surface area comparisons** ———

Glyburide
Studies in rats **with glyburide alone** at doses up to 300 mg/kg/day **(approximately 145 times the maximum recommended human dose of 20 mg for the glyburide component of** ——— for 18 months ——— ***revealed*** no carcinogenic effects.

In a two-year oncogenicity study of glyburide in mice, there was no evidence of treatment-related tumors.

There was no evidence of a mutagenic potential of glyburide alone in the following *in vitro* tests: *Salmonella* microsome test (Ames test) and in the DNA damage/alkaline elution assay.

Pregnancy

Teratogenic Effects: Pregnancy Category B

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose as close to normal as possible. Because animal reproduction studies are not always predictive of human response, should not be used during pregnancy unless clearly needed. (See below).

There are no adequate and well-controlled studies in pregnant women with or its individual components. **No animal studies have been conducted with the combined products in The following data are based on findings in studies performed with the individual products.**

Metformin hydrochloride

Metformin **alone** was not teratogenic in rats **or** rabbits at doses up to 600 mg/kg/day. **This represents an exposure of** about two **and six** times the maximum recommended human daily dose dose **of 2000 mg of the metformin component of TRADENAME based** on a body surface area **comparisons, for rats and rabbits, respectively.** Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Glyburide

Reproduction studies **were** performed in rats and rabbits at doses up to 500 times the **maximum recommended** human dose dose **of 20 mg of the glyburide component of based** on a body surface area **comparisons** and revealed no evidence of impaired fertility or harm to the fetus due to glyburide.

Nonteratogenic Effects

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. It is not recommended that be used during pregnancy. However, if it is used, should be discontinued at least two weeks before the expected delivery date. (See Pregnancy; Teratogenic Effects: Pregnancy Category B.)

Nursing Mothers

Studies in lactating rats show that metfomin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Although it is not known whether glyburide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for

hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue ———— taking into account the importance of the drug to the mother, if ———— is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

OVERALL SUMMARY AND EVALUATION:

Introduction: The sponsor initiated contact with the agency regarding development on October 17, 1996. At that time, there was no clear policy on preclinical testing of fixed combination drugs. It was determined that since there was extensive use of the combined products (as separate entities) that no preclinical studies were necessary provided that the chemistry showed that there was no interaction of the drugs when combined and stored in a single tablet. The sponsor has provided no new preclinical data and cites the previously approved NDA's for support for preclinical sections of the label. This reviewer has tried to clarify and update the proposed labeling for the fixed combination product. Note, however, that due to lack of data in previous NDA reviews, it was not possible to bring this label up to current labeling standards for some sections. Where this was not possible, statements from the approved labels are maintained.

Safety Evaluation: Pharmacology has no objection to the approval of this combination product provided chemistry demonstrates that there is no interaction of the components upon storage that might induce formation of significant levels of degradation products.

Clinical Relevance of Safety Issues: The combination of these products has been used commonly clinically.

Conclusions: Pharmacology recommends approval pending acceptance of proposed label changes.

COMMUNICATION REVIEW: see label recommendations above.
Labeling Review (NDA): see label recommendations above.
Investigator's Brochure/Informed consent review (IND): Not applicable

RECOMMENDATIONS:

Internal comments: Doses of the individual components of the fixed combination product fall within the current clinical use of the approved separate products. Pharmacology recommends approval of NDA-21-178, Metformin/Glyburide fixed combination 500/5 mg, 500/2.5 mg and 250/1.25 mg pending appropriate labeling changes as outlined below.

External Recommendations (to sponsor): Communicate labeling recommendations as listed below.
Future development or NDA issues: none.

Carcinogenisis, Mutagenesis, Impairment of Fertility.

No animal studies have been conducted with the combined products in TRADENAME. The following data are based on findings in studies performed with the individual products.

Metformin Hydrochloride

Long-term carcinogenicity studies were performed with metformin alone in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg of the metformin component of TRADENAME based on body surface area comparisons. No evidence of carcinogenicity with metformin alone was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin alone in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day of metformin alone.

There was no evidence of a mutagenic potential of metformin alone in the following *in vitro* tests: Ames test *(S. typhimurium),* gene mutation test (mouse lymphoma cells); or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin alone when administered at doses as high as 600 mg/kg/day which is approximately three times the maximum recommended human daily dose of the metformin component of TRADENAME based on body surface area comparisons.

Glyburide

Studies in rats with glyburide alone at doses up to 300 mg/kg/day (approximately 145 times the maximum recommended human dose of 20 mg for the glyburide component of TRADENAME based on body surface area comparisons) for 18 months revealed no carcinogenic effects. In a two-year oncogenicity study of glyburide in mice, there was no evidence of treatment-related tumors.

There was no evidence of a mutagenic potential of glyburide alone in the following *in vitro* tests: *Salmonella* microsome test (Ames test) and in the DNA damage/alkaline elution assay.

Pregnancy

Teratogenic Effects: Pregnancy Category B

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose as close to normal as possible. Because animal reproduction studies are not always predictive of human response, TRADENAME should not be used during pregnancy unless clearly needed. (See below).

There are no adequate and well-controlled studies in pregnant women with TRADENAME or its individual components. No animal studies have been conducted with the combined products in TRADENAME. The following data are based on findings in studies performed with the individual products.

Metformin hydrochloride
Metformin alone was not teratogenic in rats or rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose dose of 2000 mg of the metformin component of TRADENAME based on body surface area comparisons, for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

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Nonteratogenic Effects
Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. It is not recommended that TRADENAME be used during pregnancy. However, if it is used, TRADENAME should be discontinued at least two weeks before the expected delivery date. (See Pregnancy; Teratogenic Effects: Pregnancy Category B.)

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

/S/

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Supervisory Pharmacologist, DMEDP

cc: NDA Arch
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