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APPLICATION NUMBER:

201281Orig1s000

MEDICAL REVIEW(S)

Cross-Discipline Team Leader Review

Date	10/15/2011
From	Ilan Irony, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/ Supplement#	201281/ Original submission
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	January 19, 2011
PDUFA Goal Date	November 19, 2011
Proprietary Name / Established (USAN) names	Proprietary name pending review / linagliptin / metformin fixed dose combination
Dosage forms / Strength	Oral Tablets in the following dose strengths: Linagliptin 2.5 mg / metformin 500 mg, Linagliptin 2.5 mg / metformin 850 mg and Linagliptin 2.5 mg / metformin 1000 mg
Proposed Indication(s)	Improve glycemic control in adults patients with T2DM
Recommended:	Complete Response

1. Introduction

This is an original New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The reference listed drug is the US approved labeling for Glucophage (metformin). The NDA is for a fixed dose combination tablet (FDC) of linagliptin, a dipeptidyl peptidase 4 inhibitor (DPP4-i) and metformin, the only member of the biguanide class. Both components are approved in the US. When this NDA was submitted to FDA for review (January 2011), the original linagliptin NDA was still under review. This NDA was therefore considered as new molecular entity. Since linagliptin was approved in May 2011, the FDC NDA is no longer a new molecular entity. As a FDC between two approved products, approval is dependent on demonstration of bioequivalence (BE) between the two components (linagliptin and metformin) and the FDC, regarding specified pharmacokinetic and pharmacodynamic characteristics.

2. Background

Linagliptin is the third DPP4-i approved in the US. It improves glycemic control in patients with type 2 diabetes mellitus (T2DM) by inhibiting the inactivation of GLP-1 and GIP (incretin hormones) and prolonging the incretin effect on beta cells (serum glucose-dependent insulin stimulation) and alpha cells (glucagon suppression). GLP-1 in particular has other effects that contribute to improved glucose control in diabetics, such as appetite suppression and slowing of the rate of gastric emptying. Metformin is effective in decreasing hepatic glucose output and decreasing peripheral glucose utilization. Metformin gained a first line treatment recommendation by the American Diabetes Association and other diabetes professional organizations, and is widely used in the treatment of T2DM.

To support the approval of linagliptin under NDA 201280, the applicant has conducted Phase 2 and Phase 3 trials where the effect of linagliptin was assessed in subjects not adequately controlled with metformin alone. In addition, the applicant has demonstrated no drug-drug interaction between linagliptin and metformin. As a result of these aforementioned studies and their results, approval of a FDC for treatment of T2DM is dependent on demonstration of BE (geometric means ratio of C_{max} and AUC of linagliptin and metformin in the FDC to the same parameters measured when linagliptin and metformin are administered separately fall within an interval (e.g., 80 - 125%] that is unlikely to incur clinically significant variations). The FDC then is approved for either patients already taking both linagliptin and metformin separately, or for patients whose glycemic control remains inadequate despite treatment with either linagliptin or metformin. To allow treatment with the FDC in patients (b) (4) the applicant must show that the coadministration (or alternatively, the FDC) is more effective than each component alone, (b) (4) Such factorial study was conducted by BI and submitted under the current NDA for review.

3. CMC/Device

Refer to Dr. Markofsky's review for details of the CMC issues. CMC recommends a Complete Response, due to the Establishment Inspection recommendation. As of 11/7/11, the recommendation from the Office of Compliance/ Office of Manufacturing and Product Quality / Division of GMP Assessment was for Withhold for the (b) (4) manufacturing site, with an "Official Action Indicated" for that site.
The three dose strengths (linagliptin / metformin 2.5 mg / 500 mg, 2.5 mg / 850 mg and 2.5 mg / 1000 mg) are packaged in HDPE bottles in the following presentations: 14-count (for physician samples), 60-count (for one month supply), 180-count (for 3-month supply, and 2000-count (for mail-order pharmacies).
Besides linagliptin and metformin HCL, the drug product contains the following inactive ingredients: arginine, corn starch, copovidone, colloidal silicon dioxide, magnesium stearate, titanium dioxide, propylene glycol, hypromellose, talc, yellow ferric oxide (2.5 mg/500 mg; 2.5 mg/850 mg tablets) and/or red ferric oxide (2.5 mg/850 mg; 2.5 mg/1000 mg tablets). All of the inactive ingredients are compendial.
Refer to linagliptin NDA 201280 for linagliptin drug substance information. Metformin hydrochloride (USP) is manufactured by (b) (4) BI referenced DMF (b) (4) for the CMC information related to the metformin HCl drug substance, and based on the Chemistry reviews of this DMF, this drug substance (metformin HCl) is adequate to support this NDA (201281). BI's specification and testing procedures also comply with the USP monograph for metformin HCl.
The stability studies support an expiration-dating period of 24 months for all strengths of the tablets when stored at room temperature [25°C (77°F)], with excursions permitted between 59 °F to 86°F (15°C to 30°C) packaged in all of the proposed commercial container closure systems. Consequently, a 24 month expiry is granted.
From a CMC standpoint, the initial recommendation for approval had been based on:
• Adequate information was provided in the NDA for the synthesis, purification and controls of the drug substances
• Adequate manufacturing information to support the proposed to-be-marketed drug product
• Adequate specifications and controls for the drug product
• Satisfactory methods to support lot release and stability monitoring of the drug product
• Adequate stability package to support the recommended expiry period of the drug product.

That initial recommendation was changed to a Complete Response as a result of the Office of Compliance recommendation for Withhold for one of the manufacturing sites.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology / toxicology team recommends approval of the NDA. Please refer to Dr. Carlson's review for details.
A single, 'proof of concept' study in diabetic mice showed a slight improvement in baseline fasting glucose and improved glucose excursion after oral glucose tolerance test (oGTT) with combined linagliptin and metformin treatment compared to either drug alone. The study was

limited to one week duration. Nevertheless, the diabetic mouse study supports the clinical finding of improved blood glucose control with coadministration of linagliptin plus metformin treatment over monotherapy treatments.

Nonclinical toxicology studies were conducted with coadministration of linagliptin and metformin, where linagliptin was given once daily. These studies did not identify any efficacy or safety endpoints that may be affected by a change from QD to BID dosing of linagliptin (same $AUC_{0\text{-}24h}$, with lower C_{max} compared to QD dosing).

Pivotal toxicity studies were conducted to bridge potential toxicity of the coadministration of linagliptin and metformin. No unexpected toxicity or significant supra-additive or synergistic interactions attributed to coadministration were identified that would alter previous pharmacology and toxicology conclusions about the safe use of linagliptin and metformin in the treatment of T2DM. Toxicity in nonclinical studies was driven by metformin, as expected based on dosing ratios and large safety margins with linagliptin. Major target organs of metformin were heart and liver, as evidenced by heart hypertrophy with immune cell infiltration/inflammation and liver hypertrophy with concomitant hepatic injury and elevated liver enzyme biomarkers, starting at approximately 10-times the expected clinical AUC exposures. Linagliptin coadministration did not have any apparent effect on heart, liver or other metformin-related toxicity on target organs including stomach and GI tract, salivary glands, lymphoreticular tissues, or reproductive tissues.

No carcinogenicity studies were conducted with linagliptin and metformin coadministration. Neither linagliptin nor metformin are genotoxic and neither is considered to pose a significant carcinogenic risk at clinical exposures. Several linagliptin impurities, including potential or theoretical impurities and degradants, were identified and adequately qualified to show no significant toxicologic or carcinogenic risk. No further carcinogenicity testing with the combined drugs is necessary.

A notable new toxicity issue was identified in the nonclinical program suggesting potential metformin-induced teratogenicity. Metformin is not listed as teratogenic at approximate clinical exposures (estimated based on body surface area) in current labels. Studies conducted by BI clearly demonstrated that metformin at 10- to 20-times human exposure caused skeletal malformations in Wistar Han rats (a rat species often used in European toxicology studies). The studies confirmed that metformin is not teratogenic at approximate clinical exposures (clear NOAELs were established). Linagliptin combination treatment did not have any remarkable effect on the metformin-related malformations. The use of Wistar Han rats seems significant because most embryofetal development studies are conducted in Sprague Dawley (SD) rats. The reference Glucophage® label does not note the rat strain used but it seems clear from the original pharmacology/toxicology review(s) that SD rats were used. Wistar rats are reported to be more sensitive to heart malformations than SD rats and they seem to be more susceptible to the rib and scapula malformations seen with metformin treatment. More importantly, metformin was clearly toxic to pregnant rats at the teratogenic doses, causing reduced body weight gain, modestly reduced plasma glucose (albeit not to marked hypoglycemic levels), and signs of metabolic acidosis (e.g., urine pH and serum electrolyte changes). Body weight decrements typically cause developmental delays (e.g., delayed skeletal ossification), but even maternal body weight loss does not seem to cause fetal malformations in rats. On the other hand, both hypoglycemia and metabolic acidosis are known to cause fetal malformations. Importantly, data from other DPP4 inhibitor development programs coadministered with metformin do not confirm metformin-induced skeletal malformations.

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