CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Division Director's Memo

Date	May 2, 2011
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	201280
Applicant Name	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	July 2, 2010
PDUFA Goal Date	May 2, 2011
Proprietary Name / **Established (USAN) Name**	Tradjenta/Linagliptin
Dosage Forms / Strength	5 mg tablets
Proposed Indication(s)	To improve glycemic control in adults with T2DM as an adjunct to diet and exercise
Action/Recommended Action for NME:	Approval

1. Introduction

Linagliptin is the 5th dipeptidyl peptidase-4 enzyme inhibitor (DPP4-inhibitor) to be submitted under an NDA for the treatment of T2DM. Two other DPP4-inhibitors are currently marketed in the United States. These are Januvia (sitagliptin) and Onglyza (saxagliptin), and their fixed-dosed combinations with metformin, Janumet or Kombiglyze XR, respectively.

This is a relatively new class of anti-diabetic therapy whose mechanism of action targets the impaired release and availability of the incretin hormone, glucagon-like peptide-1 (GLP-1) in patients with type 2 diabetes. GLP-1 and another incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), are released from the gastrointestinal tract in response to meals to further stimulate insulin release. Because GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase 4, an inhibitor of this enzyme will prolong the half-life of this incretin hormone allowing for a more sustained effect on glucose control.

Unlike other anti-diabetic therapies, which control hyperglycemia through stimulation of insulin release from the pancreas (e.g. sulfonylureas or glinides), incretin-based therapies control hyperglycemia through a glucose-dependent manner thereby mitigating the risk of hypoglycemia. GLP-1 receptor agonists are another class of incretin-based therapies. These agents are manufactured to avoid susceptibility to enzyme degradation while maintaining sufficient cross-reactivity with the GLP-1 receptor to impart similar effects on glucose control as the native hormone. Two GLP-1 receptor agonists are currently marketed: Byetta (exenatide) and Victoza (liraglutide).

2. Background

The clinical development program for linagliptin was typical for most anti-diabetic therapies approved in the past 5 years. Monotherapy trials evaluated the drug's safety and efficacy profile in treatment-naïve T2DM population or patients with fairly recent diagnosis of T2DM who could be controlled on a single drug regimen. In addition, combination therapy with linagliptin added to several approved anti-diabetic therapies was assessed in multiple trials and a single head-to-head trial comparing linagliptin to glimepiride was conducted. This latter trial provides the longest duration of controlled efficacy and safety data for linagliptin in this NDA.

All new anti-diabetic therapies are now required to provide evidence to assure FDA that the new therapy is not associated with an adverse cardiovascular profile. Guidance for Industry outlining these recent changes to diabetes drug development programs was issued in December 2008. As a result, several development programs that were in the midst of Phase 2/3 clinical trials were required to make adjustments to their CV risk assessment plans. Boehringer Ingelheim's linagliptin was among these programs and the company presented to the FDA its proposal to evaluate CV risk from its ongoing Phase 2/3 trials. Although the inception of these trials was not with the recent guidance in mind, the trials were either early in initiation or not yet initiated such that a prospective plan for CV events adjudication and a meta-analytic plan could be implemented with FDA feedback/comments. Prior to submission of the NDA the applicant notified the FDA of its preliminary findings from its meta-analysis. Although the data appeared reassuring of CV safety, the limitations of the trials and the few CV events still required the conduct of a clinical trial prospectively designed to meet the standards set forth in the December 2008 Guidance.

This memo serves to highlight the key findings of the multiple disciplines involved in review of the NDA. In addition to evaluating the efficacy and safety of this new anti-diabetic therapy, with particular scrutiny of CV safety data, other disciplines have focused on the product manufacturing process and quality, nonclinical evaluation of known class safety concerns and to identify any unique toxicities of linagliptin, and clinical evaluation of the drug's metabolism and pharmacokinetic profile under multiple scenarios of use. In addition, all such materials have been considered in the review of the drug product's label and prescribing information.

In each section of this memo, the reader is referred to specific discipline reviews for a detailed discussion of their findings.

3. CMC/Device

CMC reviewers have recommended approval of linagliptin. Please see the reviews of Drs. Markofsky and Al-Hakim dated 2 February and 7 March 2011 for details. An acceptable establishment inspection report of manufacturing and testing facilities was issued on 15 February 2011.

Linagliptin will be available as a 5-mg, immediate-release film coated tablet in the following package presentations: 60 cc HDPE bottles containing 30 or 90 tablets; 375 cc HDPE bottles

containing 1000 tablets; and physician samples as aluminum push-through blister packets containing 7 tablets. The commercial container systems have a 30-month expiry when stored at room temperature with excursions between 15-30^{o}C permitted.

Linagliptin has one chiral center with the R-enantiomer (b) (4) being the predominant enantiomer that is also considered the active ingredient. Linagliptin also exists as (b) (4) .

The commercial formulation and investigational formulations differ only in the following: (b) (4) The biopharmaceutics review considered these to be Level 1 changes in accordance with SUPAC-IR guidance and no further comparative studies (dissolution testing or BE studies) were required.

4. Nonclinical Pharmacology/Toxicology

Please see Dr. David Carlson's review dated 7 March 2011 which contains the details of the pharmacology/toxicology program for linagliptin. Dr. Todd Bourcier's secondary review dated 10 March 2011 concurs with Dr. Carlson's assessment and both have recommended approval from pharmacology/toxicology perspective.

Linagliptin, its metabolite, and impurities were adequately studied in the nonclinical program. Pivotal repeat-dose toxicity studies were conducted in rats and monkeys and provided evidence of a wide safety margin. In the 6-month rat study, histopathology findings identified the kidney, liver, lung, stomach, and thyroid to be target organs of toxicity at doses ≥ 100 mg/kg. The histopathology findings are summarized in a table on page 54 of Dr. Carlson's review. In the 12-month monkey study there was one death of a female (1/4) at the highest dose tested 100 mg/kg/day. The cause of death was deemed kidney-related. Both males and females had evidence of delayed sexual maturation at this dose, as evidenced by decrease reproductive organ weights and decreased corpora lutea (females).

Studies exceeding 6 months in rats, including the 2-year carcinogenicity study, provided safety margins exceeding 50-times clinical exposures. Three and 12-month studies in monkeys provided safety margins exceeding 40-times clinical exposures. The exposures corresponding to the above toxicities were ≥ 54,650 nM*h in the rat and 125,000 nM*h in the monkey. In contrast, clinical exposures at steady-state is approximately 158 nM*hr for the proposed daily dosing of 5 mg.

Linagliptin is not mutagenic or clastogenic. Two impurities were identified positive on Ames testing (one was also clastogenic); however, Dr. Carlson noted that human exposure estimates for the impurities are below levels that which would pose a carcinogenic risk. Carcinogenicity studies established a NOAEL for neoplasms in male and female rats at 418x MRHD and 271x MRHD for male mice and 34x MRHD for female mice. No treatment difference in survival was noted in these studies. There were no statistically significant increases in tumor incidence

between treatment and control in the rat carcinogenicity study. There was a statistically significant increase in incidence of malignant lymphoma in female mice only at the highest dose (80 mg/kg/day ~ 287x MRHD). Given that no other drug-related tumors were observed in rats and male mice and the lymphoma finding was limited only in female mice at a 34-fold safety margin, this finding is unlikely to be of clinical relevance.

Reproductive/fertility studies also established wide safety margins for linagliptin and both Drs. Carlson and Bourcier support pregnancy category B labeling. Linagliptin crosses the placenta and is secreted in breast milk. These findings will also be reflected in labeling.

Safety findings of special interest for the class of DPP4-inhibitors include: pancreatitis (signal arising from AERS reports for Januvia and a GLP-1 analog, Byetta); cutaneous lesions (from nonclinical program of vildagliptin, a DPP4 inhibitor marketed outside the U.S.); and hypersensitivity reactions which will be further discussed under the Clinical Safety section of this memo.

Overall, the nonclinical findings have identified toxicities that occur at very high exposures yielding a wide clinical safety margin. As noted by Dr. Bourcier, these safety margins would also cover the susceptible patient population that may have higher than expected drug exposures. I concur with their assessment that nonclinical findings support approval and no nonclinical postmarketing required studies are needed at this time.

5. Clinical Pharmacology/Biopharmaceutics

There were 24 Phase 1 (20 in healthy, 2 in T2DM, 1 in renal impaired, 1 in hepatic impaired), four Phase 2, and 9 Phase 3 clinical trials and several *in vitro* ADME studies conducted in support of this NDA.

Absorption of linagliptin occurs (b) (4) with Cmax ranging between 0.5 and 3 hrs post-dosing. The extent of absorption was unaffected by food but the Cmax had a clinically insignificant 14% reduction. Linagliptin is not metabolized extensively with approximately 90% excreted unchanged in the feces and 5% excreted unchanged in the urine. Non-linear pharmacokinetics is displayed with less than dose-proportional increase in exposure at doses of 1 to 10 mg and dose-proportional increase in exposure at doses exceeding 25 mg.

Dose-Response/Dose-Selection

Several doses of linagliptin were tested in Phase 1 and 2 trials resulting in the selection of the single daily dose of 5 mg for Phase 3 development and proposed marketing. In particular, two 12-week, Phase 2 studies compared linagliptin across doses of 0.5 mg, 1.0 mg, 2.5 mg, 5 mg and 10 mg to placebo. These two studies also included active comparisons to metformin or glyburide.

Study 1218.5 was a 12-wk, randomized, double-blind, placebo-controlled trial in 302 T2DM patients who were drug-naïve or were treated with one or two oral agents and who had HbA1c 7.5-10% at screening. Patients were randomized to linagliptin 0.5, 2.5, 5 mg, placebo, or metformin. The objective of this study was to compare efficacy and safety of several doses of

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