

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208026Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 5, 2016

To: Jean-Marc Guettier, MD
Director
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Through: LaShawn Griffiths, MSHS-PH, BSN, RN
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From: Sharon W. Williams, MSN, BSN, RN
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Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): JENTADUETO XR (linagliptin and metformin hydrochloride)

Dosage Form and Route: extended-release tablets, for oral use

Application Type/Number: NDA 208026

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On July 27, 2015, Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application for JENTADUETO XR (linagliptin and metformin hydrochloride) extended-release tablets. The purpose of the submission is to seek approval for the extended release form for JENTADUETO (linagliptin and metformin hydrochloride) tablets which are currently approved.

JENTADUETO XR (linagliptin and metformin hydrochloride) extended-release tablets are used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on July 31, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for JENTADUETO XR (linagliptin and metformin hydrochloride) extended-release tablets.

2 MATERIAL REVIEWED

- Draft JENTADUETO XR (linagliptin and metformin hydrochloride) extended-release tablets MG received on July 27, 2015, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on April 29, 2016.
- Draft, JENTADUETO XR (linagliptin and metformin hydrochloride) extended-release tablets Prescribing Information (PI) received on July 27, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 29, 2016.
- Approved JENTADUETO (linagliptin and metformin hydrochloride) tablet labeling dated April 28, 2015.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON W WILLIAMS
05/05/2016

CHARUNI P SHAH
05/05/2016

SHAWNA L HUTCHINS
05/05/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Memorandum

Date: April 28, 2016 **Date consulted:** July 31, 2015

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
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Through: Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Metabolic and Endocrine Products (DMEP)

Drug/NDA: Jentaduetto XR (linagliptin and metformin hydrochloride extended-release),
NDA 208026

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of adults with Type 2 Diabetes Mellitus

Materials

Reviewed:

- DPMH consult request dated July 31, 2015, DARRTS Reference ID 3800707.
- Sponsor's submitted background package for NDA 208026, Linagliptin/Metformin XR
- DPMH review of pioglitazone products. March 9, 2016. Miriam Dinatale, D.O. and Christos Mastroyannis, M.D. DARRTS Reference ID 3898973.
- DPMH addendum of pioglitazone products. April 28, 2016. Miriam Dinatale, D.O. and Christos Mastroyannis, M.D. DARRTS Reference ID 3921521.

Consult Question:

DMEP requests DPMH to review the applicant's proposed labeling and confirm that the PLLR format is acceptable.

INTRODUCTION

The Division of Metabolic and Endocrine Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate labeling of the pregnancy and lactation subsections of Jentadueto XR labeling to comply with the Pregnancy and Lactation Labeling Rule format.

REGULATORY HISTORY

On July 27, 2015, Boehringer Ingelheim Pharmaceuticals, Inc.(BIPI), submitted a 505 (b)(1) New Drug Application (NDA 208026) for Jentadueto XR (linagliptin/metformin extended-release) for the proposed indication of treatment of adults with type 2 diabetes mellitus. The reference listed drugs include: Tradjenta (linagliptin), NDA 201280, approved May 2, 2011; Glumetza (metformin hydrochloride), NDA 021748, approved June 3, 2005, and Jentadueto (linagliptin/metformin), NDA 201281, approved January 30, 2012.

BACKGROUND**Diabetes and Pregnancy**^{1,2,3,4,5,6,7}

Diabetes mellitus (DM) complicates approximately 4% of all pregnancies in the United States. Poorly controlled DM during pregnancy increases the risk for maternal complications, including diabetic ketoacidosis, preeclampsia, spontaneous abortions (SAB), preterm delivery, stillbirth and cesarean section (due to fetal macrosomia).

Poorly controlled DM during pregnancy increases the risk for fetal malformations, including neural tube defects (anencephaly, open spina bifida, and holoprosencephaly), cardiovascular anomalies (ventricular septal defects and transposition of the great vessels), oral clefts, genitourinary abnormalities (absent kidneys, polycystic kidney, and double ureter), and sacral agenesis or caudal regression. The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HemoglobinA1c>7 and has been reported to be as high as 20-25% in women with a Hemoglobin A1c>10. In addition, poorly controlled DM may result in fetal complications, including macrosomia-related injuries (brachial plexus injury, hypoxia), fetal hypoglycemia, and respiratory distress. However, achieving and maintaining maternal euglycemia prior to conception and throughout pregnancy decreases the risk of adverse outcomes for both the mother and the infant.

¹ Mills JL. Malformations in infants of diabetic mothers. *Teratology*.1982;25:385-94

² Persson, M. and Fadi, H. Perinatal outcome in relation to fetal sex in offspring to mothers with pre-gestational and gestational diabetes- a population-based study. *Diabetes Med*. 2014; 31(9): 1047-54.

³ www.cdc.gov. Problems of Diabetes in Pregnancy. Accessed 12/30/2015.

⁴ ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. 2005; 60:675-685.

⁵ Organization of Teratology Information Specialists (OTIS) Fact Sheet. MotherToBaby.org. Accessed 3/9/2016.

⁶ Allen, Victoria, et al. Teratology Associated with Pre-Existing and Gestational Diabetes. *SOGC Practice Guidelines*. 2007; 200: 927-934.

⁷ E. Albert Reece, John C. Hobbins. *Handbook of Clinical Obstetrics: The Fetus & Mother*, Third Edition. 2007. Blackwell Publishing Ltd.

Linagliptin and Drug Characteristics⁸

Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. DPP-4 is an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). Linagliptin increases the concentrations of active incretin hormones, stimulates the release of insulin and decreases the levels of glucagon. Linagliptin has a molecular weight of 472 Daltons, is 70-80% protein bound and has a half-life of 12 hours.⁹

Metformin and Drug Characteristics¹⁰

Metformin is a biguanide that improves glucose tolerance in patients with type 2 diabetes by lowering basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin has a molecular weight of 165.65 Daltons, a plasma elimination half-life of six hours, and does not bind to proteins. Serious adverse events that have occurred with use of metformin include: lactic acidosis and impairment of renal function.

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹¹ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹² format to include information about the risks and benefits of using these products during pregnancy and lactation.

LITERATURE REVIEW

Nonclinical Experience

In animal reproduction studies performed with linagliptin/metformin administered to pregnant rats during the period of organogenesis at doses similar to clinical exposure, there was no evidence of adverse developmental effects. There was no evidence of adverse developmental effects with administration of linagliptin to pregnant rats and rabbits during the period of organogenesis at doses 943 and 1943-times, respectively, the clinical dose. In addition, there was no evidence of adverse developmental effects with administration of metformin to pregnant rats and rabbits during the period of organogenesis at doses 3 and 6- times the maximum recommended human dose, respectively. The reader is referred to the full Pharmacology/Toxicology review by David Carlson, Ph.D.

⁸ Tradjenta (linagliptin) Labeling. Section 12: Clinical Pharmacology. Drugs @FDA. Accessed 10/29/2015

⁹ <http://www.drugbank.ca/drugs/db00422>. Accessed 2/16/2015

¹⁰ Glumetza (metformin hydrochloride XR) Labeling. Section 12: Clinical Pharmacology. Drugs @FDA. Accessed 10/29/2015

¹¹ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

¹² *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

Linagliptin and Pregnancy

The applicant performed a literature search in Medline and Embase covering the period between 1995 and August 24, 2015 to identify published literature on pregnancy-related publications for linagliptin/metformin or linagliptin. However, there was no relevant information that discussed the use of linagliptin during pregnancy.

In clinical trials, there were four cases of exposure to linagliptin/metformin during pregnancy. The pregnancy outcomes were known in three out of the four cases and included three elective abortions (one due to holoprosencephaly, one due to the absence of a fetal heartbeat, no reason identified for the third abortion).

In addition, there were two reports of pregnancy during linagliptin or linagliptin/metformin use in the Boehringer Ingelheim global safety database. In one case the father was exposed to linagliptin/metformin during conception, but the outcome of the pregnancy was not known. In the second case, a female patient was exposed to linagliptin/metformin and was switched to insulin half-way through her pregnancy. She had a normal fetal ultrasound, and the outcome of the pregnancy was not reported.¹³

In addition to the search of published literature and pharmacovigilance databases performed by the applicant, DPMH also conducted a literature search in PubMed and Embase and the TERIS and ReproTox databases¹⁴ for linagliptin and use in pregnancy. No adequate and well-controlled studies of linagliptin have been conducted in pregnant women, and there were no additional human data that discussed the use of linagliptin during pregnancy.

Linagliptin and Lactation

Nonclinical studies demonstrated that linagliptin is present in the milk of lactating rats in a 4:1 ratio to plasma.

No exposure to infants during breastfeeding was reported during the clinical trials for linagliptin. In addition to the search of published literature and pharmacovigilance databases performed by the applicant, DPMH also performed a search of the Drugs and Lactation Database (LactMed)¹⁵ and PubMed. There is no information in published literature about the use of linagliptin (or other drugs in the same class) during breastfeeding. LactMed states the following:

Because no information is available on the use of linagliptin during breastfeeding, an alternate drug may be preferred, especially while nursing a newborn or preterm infant.

Summary

Linagliptin is present in rat milk at up to four-fold higher concentration in maternal milk than plasma. Drug presence and accumulation in breast milk is species specific; therefore, no direct

¹³ Boehringer Ingelheim. Periodic Benefit-Risk Evaluation Report. May 3, 2014 to May 2, 2015.

¹⁴ TERIS and ReproTox databases, Truven Health Analytics, Micromedex Solutions, 2016.

¹⁵ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

relationship can be made in humans. However, the rat data appear to support active transport of drug into milk because the levels are higher in milk compared to plasma. Linagliptin has a low molecular weight (472 Daltons), a long half-life (12 hours), and low protein-binding (70-80%), characteristics that all may increase the likelihood that the drug is transferred into breast milk.¹⁶ Current Tradjenta (linagliptin) labeling¹⁷ notes that “caution should be exercised when Tradjenta is administered to a nursing woman.”

Based on recent DPMH recommendations for another DDP4 (alogliptin)¹⁸ and given the lack of lactation information for linagliptin, DPMH recommends that the following statement appear in the “Risk Summary” section of Jentadueto XR labeling:

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for JENTADUETO XR and any potential adverse effects on the breastfed (b) (4) from JENTADUETO XR or from the underlying maternal condition.

Linagliptin and Females and Males of Reproductive Potential

In animal fertility studies in rats given linagliptin at doses 943-times the clinical dose based on the Area under the Curve (AUC) exposure, there was no evidence of impaired fertility.¹⁹ The applicant performed a literature review of Medline, Embase and PubMed to identify reports of reproductive toxicity with linagliptin and linagliptin/metformin use in humans, and no reports of reproductive toxicity were found.

In addition to the search of published literature performed by the applicant, DPMH also conducted a review of published literature in PubMed and Embase to evaluate the use of linagliptin and its effects on fertility. No additional data were found.

Summary

There are no human data on the effects of linagliptin on fertility and no evidence of infertility in animal studies to inform a potential clinical risk.

Metformin and Pregnancy

Metformin is primarily used in women with pre-gestational diabetes and off-label in women with polycystic ovary syndrome (PCOS) for infertility. For treatment of pre-gestational diabetes, metformin is often continued during pregnancy and insulin is added as appropriate to the therapy regimen. In women with PCOS, metformin is often continued until the end of the first trimester, with only limited evidence to suggest that such use decreases the risks of adverse pregnancy outcomes, including first-trimester loss.²⁰ Metformin use in women with gestational diabetes and PCOS has not been approved by the U.S. Food and Drug Administration.

¹⁶ Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

¹⁷ Drugs@FDA. Tradjenta (linagliptin) Labeling. Section 8.3, Nursing Mothers. Accessed 3/25/2016.

¹⁸ DPMH addendum of pioglitazone products. April 28, 2016. Miriam Dinatale, D.O. and Christos Mastroyannis, M.D. DARRTS Reference ID 3921521.

¹⁹ Boehringer Ingelheim Pharmaceuticals, Inc proposed Jentadueto XR Labeling: Section 13, Nonclinical Toxicology.

²⁰ De Leo, et al. The administration of metformin during pregnancy reduces polycystic ovary syndrome related gestational complications. Eur J Obstet Gynecol Reprod Biol 2011; 157:63–6.

The applicant performed a literature search in Medline and Embase covering the period between 1995 and August 24, 2015 to identify published literature on pregnancy-related publications for the linagliptin and metformin combination or metformin alone. The search retrieved a total of 483 publications related to metformin monotherapy in pregnancy and reviewed 34 relevant articles. In addition to the applicant's search of published literature for information about metformin use during pregnancy, DPMH also conducted a literature search in PubMed, Embase, ReproTox, and TERIS. The results of the literature search are described below.

Metformin use in Gestational Diabetes

Overall, published literature that has evaluated metformin use for gestational diabetes has shown no clear association between metformin use in pregnancy and adverse maternal or fetal outcomes.^{21,22,23} The Metformin in Gestational Diabetes (MiG) trial was a large (n=751) randomized, open label trial comparing the use of metformin versus insulin in the treatment of gestational diabetes. The primary focus of the study was on neonatal outcomes. There was no significant difference in the primary composite outcome (neonatal hypoglycemia, respiratory distress, phototherapy need, birth trauma, 5 minute APGAR score <7 and prematurity) between the two arms (32% metformin vs 32.2% insulin [p=0.95], RR=0.99, 95% CI 0.8-1.23). There were more incidences of neonatal severe hypoglycemia (BG levels <28.8mg/dL) with insulin compared to metformin (8.1% vs 3.3%, p=0.008). There was a significant increase in the number of preterm births (<37 weeks gestation) with metformin compared to insulin (12.1% vs 7.6%, p=0.04). However, there was minimal clinical difference in mean gestational age between the two agents (38.3 weeks with metformin versus 38.5 weeks with insulin).²⁴

Since the MiG trial, nine other metformin studies (randomized control trials, case-control trials and observational studies) in women with gestational diabetes have been published. Six trials compared metformin to insulin^{25,26,27,28,29,30} and three trials compared metformin to glyburide.^{31,32,33} For all but one of the studies that compared insulin to metformin [24, 25, 26,

²¹ Langer, et al. There is no association between oral hypoglycemic use and fetal anomalies. Am J Obstet Gynecol 1999;180:S38

²² Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. Obstet Gynecol 2009; 113:193–205.

²³ Carrol, D., Kelley, K.: Review of metformin and glyburide in the management of gestational diabetes. Pharm Pract (Granada). 2014 Oct-Dec; 12(4): 528

²⁴ Rowan, J. et al. Metformin versus Insulin for the Treatment of Gestational Diabetes. The New England Journal of Medicine. 2008; 358: 2003-2015.

²⁵ Terti, et al. Comparison of metformin and insulin in the treatment of gestational diabetes: a retrospective case-control study. Rev Diabet Stu. 2008; 5 (2): 95-101.

²⁶ Balani, et al. Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin: a case-control study. Diabet Med. 2009; 26 (8):798–802.

²⁷ Ijäs, et al. Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study. BJOG. 2011; 118(7):880–885.

²⁸ Niromanesh, et al. Metformin compared with insulin in the management of gestational diabetes: a randomized clinical trial. Diabetes Res Clin Pract. 2012;98(3):422–9.

²⁹ Terti K, et al. Metformin vs insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin. Diabetes Obes Metab. 2013;15(3):246–251.

³⁰ Spaulonci, et al. Randomized trial of metformin vs insulin in the management of gestational diabetes. Am J Obstet Gynecol. 2013; 209(1):34.e1–7.

³¹ Silva, et al. Metformin compared to glyburide for the management of gestational diabetes. Int J Gynaecol Obstet. 2010;111(1):37–40.

27, 29], there were no differences in birth weight, gestational age, mode of delivery, prematurity or perinatal deaths. One trial [28] reported more infants with birth weights >90th percentile (35% versus 17.5%, $p=0.012$) and higher birth weights (3.4 kg versus 3.3kg, $p\text{-value}=0.005$) in the insulin group compared to the metformin group. For trials that compared metformin to glyburide, there was no difference in maternal blood glucose, neonatal hypoglycemia, macrosomia or gestational age of delivery.

The American College of Obstetrics and Gynecology (ACOG) recently updated its position statement regarding the use of oral medications in the treatment of gestational diabetes and noted that both glyburide and metformin have favorable safety profiles.³⁴

Metformin Use in PCOS and Type 2 Diabetes Mellitus

Data from PCOS and Type 2 Diabetes Mellitus (i.e., DM that was present prior to pregnancy) studies provide information on the effects of metformin use in the first trimester of pregnancy. Published observational studies do not report a clear association with metformin use in the first trimester of pregnancy and major birth defects, miscarriage or adverse perinatal outcomes (decreased fetal growth, neonatal hypoglycemia).^{35,36,37,38,39,40}

There are two studies that have demonstrated an increase in complications with metformin use during pregnancy.

- In a retrospective cohort study (Hellmuth, *et al*), the authors found that the prevalence of pre-eclampsia was increased in the metformin group compared to the sulfonylurea and insulin groups (32% versus 7% versus 10%, $p\text{-value}<0.001$). There was also an increase in perinatal mortality in the metformin group versus women not treated with metformin (11.6% versus 1.3%, $p\text{-value}<0.02$).⁴¹
- In a multicenter, observational prospective cohort study (Panchaud, *et al.*), major congenital anomalies were more frequent among the infants of 323 women who had used metformin during pregnancy than among control infants (7.6% vs. 2.5% respectively; odds ratio=3.2, 95% confidence interval 1.3-9.2, $p=0.005$). However, the authors noted that there is a potential for confounding effects of the underlying metabolic disease and

³² Moore, et al. Metformin compared with glyburide in gestational diabetes. *Obstet Gynecol.* 2010;115(1):55–59.

³³ Silva JC, Fachin DR, Coral ML, Bertini AM. Perinatal impact of the use of metformin and glyburide for the treatment of gestational diabetes mellitus. *J Perinat Med.* 2012;40(3):225–228.

³⁴ Practice Bulletin No. 137: Gestational diabetes mellitus. Committee on Practice Bulletins--Obstetrics. *Obstet Gynecol.* 2013 Aug;122(2 Pt 1):406-16

³⁵ Bolton, et al. Continuation of metformin in the first trimester of women with polycystic ovarian syndrome is not associated with increased perinatal morbidity. *Eur J Pediatr.* 2009;168(2):203–206

³⁶ Gilbert C, Valois M, Koren G. Pregnancy outcomes after first trimester exposure to metformin: a meta-analysis. *Fertil Steril.* 2006 Sep;86(3):658–663

³⁷ Briggs GG, editor. 9th edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2011. Metformin. *Drugs in Pregnancy and Lactation*; pp. 912–915

³⁸ Diav-Citrin, O.; Steinmetz-Shoob, S.; Shechtman, S. and Ornoy, A.: Pregnancy outcome following *in utero* exposure to metformin: A prospective comparative observational study. *Birth Defects Res. A Clin. Mol. Teratol.* 100(7):520, 2014

³⁹ Glueck CJ, et al. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod.* 2002 Nov;17(11):2858-64.

⁴⁰ Coetzee, E.J. and Jackson, W.P.U.: Oral hypoglycemics in the first trimester and fetal outcome. *S. Afr. Med. J.* 65:635-637, 1984

⁴¹ Hellmuth, et al. Oral hypoglycaemic agents in 118 diabetic pregnancies. *Diabetic Medicine.* 2000; 17: 507-511.

that further data collection and analysis of potential bias was being undertaken at the time the results of the study were published.⁴²

Reviewer comments:

In the study by Hellmuth, et al. the women in the metformin group were more likely to be obese (pre-pregnancy BMI was 31.2 compared to 22.8 and 24.8 in the sulfonylurea and insulin groups, respectively). An obese or overweight patient with type 2 diabetes is at an increased risk of preeclampsia, cesarean delivery, shoulder dystocia, preterm delivery, large-for-gestational age infant, fetal malformations and admission of the infant into the neonatal intensive care unit. Therefore, it is difficult to determine whether the increased prevalence of pre-eclampsia was due to metformin use or due to obesity.^{43,44}

In the study by Panchaud, et al., the metformin-exposed population was made up of patients with pre-gestational diabetes, but the control population was made up of non-diabetic patients. Having a diabetes diagnosis increases the risk of congenital malformations, and it is likely that increased rate of congenital malformations seen in the metformin-exposed pregnancies was due to the underlying diabetes and not necessarily due to metformin use during pregnancy.

See the previous DPMH reviews^{45,46} by Miriam Dinatale, D.O. and Christos Mastroyannis, M.D. for a complete review of published studies that evaluated the use of metformin during pregnancy.

Summary

Overall, published safety data from controlled trials and post-marketing observational studies do not report a clear association with major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Metformin and Lactation

The applicant performed a literature search in Medline and Embase covering the period between 1995 and August 24, 2015 to identify published literature on lactation-related publications for metformin and retrieved two publications. In addition to the applicant's search of published literature for information about metformin use during lactation, DPMH also performed a search of the Drugs and Lactation Database (LactMed)⁴⁷ and PubMed and Embase.

⁴² Panchaud, A et al. Pregnancy outcome following maternal exposure to metformin: Preliminary results of a collaborative ENTIS and Motherisk study. Birth Defects Res. A Clin. Mol. Teratol. 100(7):521, 2014

⁴³ www.cdc.gov. Reproductive Health: Maternal and Infant Health and Pregnancy Complications. Accessed 12/18/2015.

⁴⁴ Racusin, et al. Obesity and the Risk and Detection of Fetal Malformations. Seminars in Perinatology. 2012; 36(3): 213-221.

⁴⁵ DPMH review of pioglitazone products. March 9, 2016. Miriam Dinatale, D.O. and Christos Mastroyannis, M.D. DARRTS Reference ID 3898973.

⁴⁶ DPMH addendum of pioglitazone products. April 28, 2016. Miriam Dinatale, D.O. and Christos Mastroyannis, M.D. DARRTS Reference ID 3921521.

⁴⁷ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels,

LactMed notes that data from clinical lactation studies demonstrate that metformin levels in breast milk are low and that “metformin should be used with caution when women are breastfeeding neonates and premature infants, especially those with renal impairment.”

In a lactation study (Eyal, *et al.*), breast milk samples were collected from four women with either PCOS or diabetes (Type 2 diabetes mellitus or gestational diabetes) who were treated with metformin (1500 mg/day in one patient; 2000 mg/day in three patients) in the post-partum period. The amounts of metformin detected in breast milk daily were 0.13, 0.15, 0.21 and 0.28 mg with corresponding relative infant doses of 0.21, 0.14, 0.21 and 0.43% of the mother’s weight adjusted dose, respectively. Maternal and infant serum samples were not collected, and there was no information about any effects of metformin on the infant.⁴⁸

See the previous DPMH review⁴⁹ by Miriam Dinatale, D.O. and Christos Mastroyannis for a complete review of other lactation studies^{50,51,52,53,54,55,56} that were performed in women taking metformin.

Summary

Metformin is present in breast milk in low levels. In a review of published literature of metformin use during lactation, the milk-to-plasma ratio ranged between 0.13 to 1, and the relative infant dose ranged between 0.11 to 1%.. A drug that has a milk-to-plasma ratio that is less than one is considered safe to use while breastfeeding.⁵⁷ A drug with a relative infant dose of less than 10% of the maternal dose, is considered safe for use during breastfeeding.⁵⁸ Metformin did not appear to have any adverse effects on two breastfed infants that were evaluated by physicians in the lactation study by Hale, *et al.* However, there is limited information on the effect of metformin on a breastfed infant.

any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

⁴⁸ Eyal S, Easterling TR, Carr D, et al. Pharmacokinetics of metformin during pregnancy. *Drug Metabolism & Disposition*. 2010 May; 38(5):833-40

⁴⁹ DPMH review of pioglitazone products. March 9, 2016. Miriam Dinatale, D.O. and Christos Mastroyannis, M.D. DARRTS Reference ID 3898973.

⁵⁰ Hale TW, et al. Transfer of metformin into human milk. *Diabetologia*. 2002; 45:1509-14.

⁵¹ Hale T, et al. Transfer of metformin into human milk. *Adv Exp Med Biol*. 2004; 554:435-6.

⁵² Gardiner SJ, Kirkpatrick CM, Begg EJ et al. Transfer of metformin into human milk. *Clin Pharmacol Ther*. 2003;73:71-7

⁵³ Briggs GG, Ambrose PJ, Nageotte MP et al. Excretion of metformin into breast milk and the effect on nursing infants. *Obstet Gynecol*. 2005;105:1437-41.

⁵⁴ Glueck CJ, Salehi M, Sieve L, Wang P. Growth, motor, and social development in breast- and formula-fed infants of metformin-treated women with polycystic ovary syndrome. *J Pediatr*. 2006;148:628-32.e2

⁵⁵ Thatcher SS, Jackson EM. Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin. *Fertil Steril*. 2006;85:1002-9

⁵⁶ Vanky E, Nordskar J, Leithe H et al. Breast size increment during pregnancy and breastfeeding in mothers with polycystic ovary syndrome: a follow-up study of a randomised controlled trial on metformin versus placebo. *BJOG*. 2012;119:1403-9

⁵⁷ Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. *Journal of the American Pharmacists Association*. 2012; 51 (1): 86-94.

⁵⁸ Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. *Journal of the American Pharmacists Association*. 2012; 51 (1): 86-94.

Metformin and Females and Males of Reproductive Potential

The applicant performed a literature review of Medline, Embase and PubMed to identify reports of reproductive toxicity with linagliptin/metformin or metformin use in humans, and no reports of reproductive toxicity were found.

In addition to the search of published literature performed by the applicant, DPMH also conducted a review of published literature in PubMed and Embase to evaluate the use of metformin and its effects on fertility. Metformin is used off-label for the treatment of PCOS and has been shown to increase ovulation and the potential for pregnancy in women taking the drug.^{59,60} There is no evidence of infertility in patients who take metformin. In animal fertility studies in rats given metformin at doses three times the MRHD, there was no evidence of impaired fertility.⁶¹

Summary

Metformin may increase ovulation and the potential for pregnancy, and women who are taking metformin-containing products should be informed of the possibility. Therefore, Section 8.3, Females and Males of Reproductive Potential, should note that metformin may result in ovulation in premenopausal anovulatory women and increase the potential for pregnancy.

CONCLUSIONS

Jentadueto XR labeling has been updated to comply with the PLLR. A review of the literature revealed no new data with linagliptin or metformin use in pregnant or lactating women. DPMH has the following recommendations for Jentadueto XR labeling:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” section of Jentadueto XR labeling was formatted in the PLLR format to include: “Risk Summary,” “Clinical Considerations,” and “Data” sections⁶².
- **Lactation, Section 8.2**
 - The “Lactation” section of Jentadueto XR labeling was formatted in the PLLR format to include: the “Risk Summary” and “Data” sections.”⁶³
- **Females and Males of Reproductive Potential, Section 8.3**
 - The “Females and Males of Reproductive Potential” section of Jentadueto XR labeling was included to discuss the increased potential for ovulation in some premenopausal anovulatory women pregnancy.⁶⁴

⁵⁹ Polycystic Ovarian Syndrome Medication. www.medscape.com. Accessed 12/31/2015.

⁶⁰ Sangeeta, S. Metformin and Pioglitazone in Polycystic Ovarian Syndrome: A Comparative Study. 2012; 62(5): 551-556.

⁶¹ Takeda proposed Actos Labeling: Section 13, Nonclinical Toxicology.

⁶² Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

⁶³ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1-Risk Summary.

⁶⁴ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

- **Patient Counseling Information, Section 17**

- The “Patient Counseling Information” section of Jentadueto XR labeling was updated to correspond with changes made to sections 8.1, 8.2, and 8.3 of labeling.

RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, 8.3 and 17 of Jentadueto XR labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. See Appendix A for the applicant’s proposed pregnancy and lactation labeling.

DPMH Proposed Jentadueto XR Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

- Females and Males of Reproductive Potential: (b) (4)
(8.3).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with JENTADUETO XR and linagliptin use in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [see Data]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see Clinical Considerations]. In animal reproduction studies, no adverse developmental effects were observed when the combination of linagliptin and metformin was administered to pregnant rats during the period of organogenesis at doses similar to clinical (b) (4), based on exposure [see Data].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c>7 and has been reported to be as high as 20-25% in women with HbA1c>10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, (b) (4) and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies do not report a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Linagliptin and metformin, the components of JENTADUETO XR, were co-administered to pregnant Wistar Han rats during the period of organogenesis. No adverse developmental outcome was observed at doses similar to the maximum recommended clinical dose, based on exposure. At higher doses associated with maternal toxicity, the metformin component of the

combination was associated with an increased incidence of fetal rib and scapula malformations at ≥ 9 -times a 2000 mg clinical dose, based on exposure.

Linagliptin

No adverse developmental outcome was observed when linagliptin was administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg and 150 mg/kg, respectively. These doses represent approximately 943 times (rats) and 1943 times (rabbits) the 5 mg clinical dose, based on exposure. No adverse functional, behavioral, or reproductive outcome was observed in offspring following administration of linagliptin to Wistar Han rats from gestation day 6 to lactation day 21 at a dose 49 times the 5 mg clinical dose, based on exposure.

Metformin Hydrochloride:

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 6-times a clinical dose of 2000 mg, based on body surface area.

8.2 Lactation

Risk Summary

There is no information regarding the presence of JENTADUETO XR or linagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. However, linagliptin is present in rat milk. Limited published studies report that metformin is present in human milk [see Data]. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JENTADUETO XR and any potential adverse effects on the breastfed (b) (4) from JENTADUETO XR or from the underlying maternal condition.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

8.3 Females and Males of Reproductive Potential

Therapy with metformin may result in ovulation in some premenopausal anovulatory women. Discuss the potential for unintended pregnancy with premenopausal women.

17 PATIENT COUNSELING INFORMATION

- Pregnancy: Inform females that treatment with metformin may result in (b) (4) unintended pregnancy in some premenopausal anovulatory females [see Use in Specific Populations (8.3)].

Medication Guide

Before you take TRADE NAME, tell your doctor if you:

- **are pregnant or plan to become pregnant.** It is not known if JENTADUETO XR can harm your unborn baby. If you are pregnant (b) (4), talk with your doctor about the best way to control your blood sugar while you are pregnant.
- **are a premenopausal woman (before the “change of life”), who does not have periods regularly or at all.** JENTADUETO XR may increase your chance of becoming pregnant. Talk to your doctor about birth control choices while taking JENTADUETO XR if you are not planning to become pregnant. Tell your doctor right away if you become pregnant while taking JENTADUETO XR.
- **are breastfeeding or plan to breast feed.** It is not known if JENTADUETO XR passes into your milk (b) (4). Talk to your doctor about the best way to feed your baby if you take JENTADUETO XR.

APPENDIX A – Applicant’s Proposed Jentaduet XR Pregnancy and Nursing Mothers Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: (b) (4)
(8.1)
- Lactation: (b) (4)
(8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

The background risk of (b) (4) miscarriage for the indicated population is unknown; however background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, and delivery complications (b) (4)

(b) (4). Poorly controlled diabetes increases the fetal risk for (b) (4) still birth, macrosomia related morbidity (b) (4)

(b) (4).

Data

Human data

(b) (4)

(b) (4)

Animal Data

(b) (4)

Linagliptin:

(b) (4)

Linagliptin was (b) (4) administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg/day and 150 mg/kg/day, respectively. These doses represent approximately 943 times the clinical dose in rats and 1943 times the clinical dose (b) (4), based on exposure. No functional, behavioral, or reproductive toxicity was observed in offspring (b) (4) Wistar Han rats (b) (4) from gestation day 6 to lactation day 21 at a dose 49 times the (b) (4) dose, based on exposure.

Metformin:

(b) (4)

(b) (4) Metformin

(b) (4) up to 600 mg/kg/day, (b) (4)

(b) (4) 6 times the (b) (4) dose of 2000 mg/kg/day based on body surface area (b) (4) (b) (4)

8.2 Lactation

Risk Summary

(b) (4)

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JENTADUETO XR and any potential adverse effects on the breastfed child from JENTADUETO XR or from the underlying maternal condition.

Data

(b) (4)

Linagliptin

(b) (4)

Metformin

(b) (4)

Medication Guide

Before you take TRADE NAME, tell your doctor if you:

- are pregnant or plan to become pregnant. It is not known if JENTADUETO XR will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breast feed. It is not known if JENTADUETO XR passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take JENTADUETO XR.

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/s/

MIRIAM C DINATALE
04/28/2016

TAMARA N JOHNSON
05/02/2016

LYNNE P YAO
05/02/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 28, 2016
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: NDA 208026
Product Name and Strength: Jentadueto XR (linagliptin and metformin hydrochloride extended-release) tablets
2.5 mg linagliptin/1,000 mg 5 mg linagliptin/1,000 mg
Submission Date: April 6, 2016
Applicant/Sponsor Name: Boehringer Ingelheim Pharmaceuticals, Inc.
OSE RCM #: 2015-1706-1
DMEPA Primary Reviewer: Sarah K. Vee, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

DMEP requested that we review the revised container label and carton labeling for Jentadueto XR (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container label and carton labeling for Jentadueto XR is acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Mistry, M. Label and Labeling Review for Jentadueto XR (NDA 208026). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAR 14. 32 p. OSE RCM No.: 2015-1706.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SARAH K VEE
04/28/2016

YELENA L MASLOV
04/29/2016

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 11, 2016

TO: Jean-Marc Guettier, MD
Director
Division of Metabolic and Endocrine Products

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Inspection of Boehringer Ingelheim Pharma GmbH & Co.
KG, covering the following application:

NDA 208026 [Linagliptin/Metformin extended release
(fixed dose combination) sponsored by Boehringer
Ingelheim, CT, USA]

Reviewer's Recommendation: This OSIS reviewer recommends that the results from clinical portions of the following studies be accepted for further Agency review. Please note that EIR reviews of bioanalytical inspections at (b) (4) were finalized in DARRTS on 02/19/2016 and 03/15/2016, respectively

The inspection was conducted by ORA Investigator Zerita White at Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, Germany, from January 21 to January 25, 2016. The clinical portions of the following bioequivalence studies were audited during the inspection:

Study #: 1288.09

Study Title: "Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (5 mg/1000 mg) compared with the free combination of linagliptin and metformin extended release tablets in healthy subjects (an open-label, randomised,

single dose, two way crossover trial)"
Study Period: May 13, 2014 - July 31, 2014

Study #: 1288.11

Study Title: "Bioequivalence of a fixed dose combination tablet
of linagliptin/metformin extended release (2.5 mg/
1000 mg) compared with the free combination of
linagliptin and metformin extended release tablets
in healthy subjects (an open-label, randomised,
single dose, two way crossover trial)"

Study Period: April 24, 2014 - July 11, 2014

The audit included a thorough review of study records, including
study protocol compliance, informed consent, institutional review
board approvals, case report forms, examination of facilities and
test article accountability, as well as interviews and
discussions with the firm's management and staff.

Following the inspection, no objectionable conditions were found
and no Form FDA-483 was issued.

Conclusions:

Following a review of the inspection report, this reviewer
recommends that results from clinical portions of the following
studies be accepted for further Agency review.

NDA 208026

Study #: 1288.09

Study #: 1288.11

Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Final Classification:

NAI: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
(**FEI:** 3002806518)

Email cc:

OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller
OSIS/DNDBE/Bonapace/Dasgupta
OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Li
CDER/OND/DMEP/Guettier
ORA/Zerita White

Draft: XFL 3/09/2016
Edits: MFS 3/09/2016; JC 3/11/2016
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/ Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

OSI file# BE6998; NDA 208026

FACTS: 11581819

Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

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/s/

XINGFANG LI
03/31/2016

SEONGEUN CHO
03/31/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 14, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208026
Product Name and Strength:	Jentaduo XR (linagliptin and metformin hydrochloride extended-release) tablets 2.5 mg linagliptin/1,000 mg metformin HCl extended-release 5 mg linagliptin/1,000 mg metformin HCl extended-release
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Date:	July 27, 2015 and March 11, 2016
OSE RCM #:	2015-1706
DMEPA Primary Reviewer:	Mishale Mistry, PharmD, MPH
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the labels and labeling for Jentadueto XR (linagliptin and metformin hydrochloride extended-release) tablets, NDA 208026, submitted on July 27, 2015 and March 11, 2016. The Division of Metabolism and Endocrinology Products requested that DMEPA review the proposed labels and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G – N/A

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety, related to preventable medication errors. We note that the proposed container and carton labels and labeling can be improved to increase the prominence of important information.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information and promote the safe use of the product and mitigate any confusion.

4.1 RECOMMENDATIONS FOR BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

1. Container Labels

- a. We recommend increasing the font size of the strength to improve prominence and readability, and to mitigate the potential for wrong strength errors.
- b. Revise the statement [REDACTED] (b) (4) to as follows to ensure consistency between Jentaduetto XR and Jentaduetto:

[REDACTED] (b) (4) ”

2. Carton Labeling

- a. See recommendations 1.b.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Jentadueto XR that Boehringer Ingelheim Pharmaceuticals, Inc. submitted on July 27, 2015.

Table 2. Relevant Product Information for Jentadueto XR	
Initial Approval Date	N/A
Active Ingredient	linagliptin and metformin hydrochloride extended-release
Indication	Adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.
Route of Administration	Oral
Dosage Form	Oral tablets
Strength	2.5 mg linagliptin/1,000 mg metformin HCl extended-release 5 mg linagliptin/1,000 mg metformin HCl extended-release
Dose and Frequency	Dose should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended daily dose of 5 mg linagliptin/2,000 mg metformin hydrochloride. Jentadueto XR should be given once daily with a meal. Recommended starting dose: • In patients currently not treated with metformin: initiate treatment with 5 mg linagliptin/1,000 mg metformin HCl extended-release once daily. • In patients already treated with metformin: total daily starting dose of 5 mg linagliptin and a similar total daily dose of metformin. • In patients already treated with Tradjenta and metformin, or Jentadueto, switch to Jentadueto XR containing 5 mg of linagliptin total daily dose and a similar total daily dose of metformin. Jentadueto XR should be swallowed while. The tablets must not be split, crushed, or chewed before swallowing.
How Supplied	2.5 mg linagliptin/1,000 mg metformin HCl extended-release: • Bottles of 60 and 180 tablets 5 mg linagliptin/1,000 mg metformin HCl extended-release: • Bottles of 30 and 90 tablets
Storage	Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]. Protect from exposure to high humidity. Store in a safe place out of reach of children.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 23, 2015, we searched the L:drive and AIMS using the terms, Jentadueto XR to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews related to the label and labeling of Jentadueto XR.

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS – N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on December 1, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.¹

Table 3: FAERS Search Strategy	
Date Range	December 1, 2015
Product	linagliptin/metformin hydrochloride [active ingredient] Jentadueto [product name]
Application Number	NDA 201281
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT)

¹ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

	Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)
--	--

E.2 Results

Our search identified 7 cases, of which 4 described errors relevant for this review.

Wrong frequency of administration (n=2):

- One case (FAERS Case ID #9180971 [v1]) reported that a patient was taking Jentadueto two 2.5 mg/500 mg tablets once daily. The patient “misunderstood directions for sample use and was taking two tablets at once, one time daily, not one tablet two times a day.” The patient experienced a “tingling/burning sensation of her lips and face approximately one hour after taking Jentadueto...symptoms would last 1-2 hours and spontaneously resolve until her next dose”.
- One case (FAERS Case ID #9585490 [v1]) reported that a patient took Jentadueto 2.5 mg / 1000 mg three times daily, instead of twice daily as directed by physician. No additional information regarding root cause, contributing factors or outcome was provided.
- Section 2.1 Recommended Dosing of the current Prescribing Information labeling for Jentadueto states “Jentadueto should be given twice daily with meals”. The proposed labeling for Jentadueto XR states “Jentadueto should be given once daily with a meal”. Upon review, the labeling information contains clear information regarding the schedule of administration for Jentadueto and Jentadueto XR. Therefore, we do not believe any revisions to the Jentadueto or Jentadueto XR labeling are needed at this time.

Improper dose (resulting in overdosage)(n=2):

- One case (FAERS Case ID #9315144 [v1]) reported that a patient was taking 4 Jentadueto tablets daily and it was unknown whether the patient took the medication intentionally or accidentally. No additional information regarding root cause, contributing factors or outcome was provided.
- One case (FAERS Case ID #9416056 [v1]) reported that a patient was taking Jentadueto 2.5 mg/500 mg twice daily at a total daily dose of 10 mg/2000 mg as the physician prescribed. No additional information regarding root cause, contributing factors or outcome was provided.

- Section 2.1 Recommended Dosing of the current Prescribing Information labeling for Jentadueto includes the statement “...while not exceeding the maximum recommended dose of 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily”. The proposed labeling for Jentadueto XR includes the statement “...while not exceeding the maximum recommended dose of (b) (4) metformin hydrochloride once daily”. Upon review, the labeling information contains clear information regarding the dose and maximum dose for Jentadueto and Jentadueto XR. Therefore, we do not believe any revisions to the Jentadueto or Jentadueto XR labeling are needed at this time.

We excluded 3 cases because they described reports of drug dose omission (n=1), product quality issues (n=1), and did not involve Jentadueto as the primary suspect product (n=1).

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case ID	Version	Manufacturer Control Number
10405596	1	US-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2014-BI-38696BP
11237032	3	US-009507513-1506USA013204
9180971	1	US-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2013-BI-06692BP
9315144	1	US-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2013-BI-14759BP
9416056	1	US-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2013-BI-21362BP
9585490	1	US-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2013-BI-30026BP
9871179	4	US-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2014-BI-04467BP

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX F. OTHER – N/A

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MISHALE P MISTRY
03/14/2016

YELENA L MASLOV
03/15/2016

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 11, 2016

TO: Jean-Marc Guettier, MD
Director
Division of Metabolic and Endocrine Products

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Inspection of Boehringer Ingelheim Pharma GmbH & Co.
KG, covering the following application:

NDA 208026 [Linagliptin/Metformin extended release
(fixed dose combination) sponsored by Boehringer
Ingelheim, CT, USA]

Reviewer's Recommendation: This OSIS reviewer recommends that the results from clinical portions of the following studies be accepted for further Agency review. Please note that EIR reviews of bioanalytical inspections at (b) (4) were finalized in DARRTS on 02/19/2016 and 03/15/2016, respectively

The inspection was conducted by ORA Investigator Zerita White at Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, Germany, from January 21 to January 25, 2016. The clinical portions of the following bioequivalence studies were audited during the inspection:

Study #: 1288.09

Study Title: "Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (5 mg/1000 mg) compared with the free combination of linagliptin and metformin extended release tablets in healthy subjects (an open-label, randomised,

single dose, two way crossover trial)"
Study Period: May 13, 2014 - July 31, 2014

Study #: 1288.11

Study Title: "Bioequivalence of a fixed dose combination tablet
of linagliptin/metformin extended release (2.5 mg/
1000 mg) compared with the free combination of
linagliptin and metformin extended release tablets
in healthy subjects (an open-label, randomised,
single dose, two way crossover trial)"

Study Period: April 24, 2014 - July 11, 2014

The audit included a thorough review of study records, including
study protocol compliance, informed consent, institutional review
board approvals, case report forms, examination of facilities and
test article accountability, as well as interviews and
discussions with the firm's management and staff.

Following the inspection, no objectionable conditions were found
and no Form FDA-483 was issued.

Conclusions:

Following a review of the inspection report, this reviewer
recommends that results from clinical portions of the following
studies be accepted for further Agency review.

NDA 208026

Study #: 1288.09

Study #: 1288.11

Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Final Classification:

NAI: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
(**FEI:** 3002806518)

Email cc:

OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller
OSIS/DNDBE/Bonapace/Dasgupta
OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Li
CDER/OND/DMEP/Guettier
ORA/Zerita White

Draft: XFL 3/09/2016
Edits: MFS 3/09/2016; JC 3/11/2016
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/ Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

OSI file# BE6998; NDA 208026

FACTS: 11581819

Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

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/s/

XINGFANG LI
03/15/2016

SEONGEUN CHO
03/15/2016

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 15, 2016

TO: Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
(DMEP)
Office of New Drugs (OND)

FROM: Li-Hong Paul Yeh, Ph.D.
Chemical Engineer
Division of New Drug Bioequivalence Evaluation
(DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Xikui Chen, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR for studies submitted to NDA 208026,
conducted at (b) (4)

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical portion of studies 1288-9 and 1288-11 at (b) (4). Please note that EIR reviews of the bioanalytical inspection at (b) (4) (b) (4) and the clinical inspection at Boehringer Ingelheim Pharma GmbH & Co, KG, Biberach/Riss, Germany, were finalized in DARRTS on 2/19/2016 and 3/15/2016, respectively.

The inspection was conducted by ORA Investigator Zerita White at Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, Germany, from January 21 to January 25, 2016. We recommend that

the bioanalytical data for metformin assays in studies 1288-9 and 1288-11 be accepted for further Agency review.

Studies Audited during this Inspection:

Study number: 1288-9 (CP145011)
Study Title: "Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (5 mg/1000 mg) compared with the free combination of linagliptin and metformin extended release tablets in healthy subjects (an open label, randomized, single dose, two-way crossover trial)"
Sample Analysis: July 29 to August 22, 2014

Study number: 1288-11 (CP145013)
Study Title: "Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (2.5 mg/1000 mg) compared with the free combination of linagliptin and metformin extended release tablets in healthy subjects (an open-label, randomized, single dose, two-way crossover trial)"
Sample Analysis: July 07 to August 5, 2014

Bioanalytical Site: (b) (4)

OSIS scientists Xikui Chen, Ph.D. and Paul Yeh, Ph.D. conducted the inspection of the bioanalytical portion of the studies from (b) (4). The audit covered the bioanalytical method validation and sample analysis for metformin. The audit included a thorough review of facilities and equipment, review of study records and correspondence, and interviews and discussions with (b) (4) management and staff. As a global assessment of the firm's bioanalytical operations, several key components in the study conduct were selected for audit to evaluate the firm's bioanalytical operations since the previous inspection.

At the conclusion of the inspection, no Form FDA 483 was issued at (b) (4).

Recommendation:

Following review of the EIR, the analytical data for studies 1288-9 and 1288-11 were found to be reliable. Therefore, we recommend that the data from the bioanalytical portion of

studies 1288-9 and 1288-11 be accepted for further Agency review.

Li-Hong Yeh, Ph.D.
DNDBE, OSIS

Xikui Chen, Ph.D.
DGDBE, OSIS

Final Classification:

NAI: (b) (4) **(Analytical)**

CC:

OTS/OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller/Kadavil

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Yeh

OTS/OSIS/DGDBE/Cho/Skelly/Choi/Chen

Draft: XC 03/11/2016

Edit: PY 03/11/2016; MFS 03/11/2016; JC 03/14/2016

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/
Bioanalytical Sites/

(b) (4)

OSIS fi (b) (4)

FACTS: (b) (4)

Attachment 1: Application covered during the inspection.

NDA Number	FEI	Location
208026	(b) (4)	

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/s/

XIKUI CHEN
03/15/2016

SEONGEUN CHO
03/15/2016

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: February 11, 2016

TO: Jean-Marc Guttier, M.D.
Director
Division of Metabolism and Endocrinology Products
(DMEP)
Office of New Drugs (OND)

Donna Griebal, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products (DGIEP)
Office of New Drugs (OND)

FROM: Li-Hong Paul Yeh, Ph.D.
Chemical Engineer
Division of New Drug Bioequivalence Evaluation (DND BE)
Office of Study Integrity and Surveillance (OSIS)

Xikui Chen, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DND BE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR for st [redacted] Non Responsive and NDA
208026 conducted at [redacted] (b) (4)
[redacted] (b) (4)

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) inspection of the bioanalytical portion of studies [redacted] Non Responsive
[redacted] 1288-0009 and 1288-0011 at [redacted] (b) (4)
[redacted] (b) (4). At the conclusion of the inspection, a one-item Form
FDA 483 was issued. The final classification for [redacted] (b) (4)
[redacted] (b) (4) is voluntary action indicated (VAI). We recommend that the

data for the bioanalytical portion of studies (b) (4) 1288-0009 (except run 20) and 1288-0011 be accepted for further agency review.

Studies Audited During This Inspection:

Non Responsive

NDA 208026

Study#2: 1288-0009 (1288.9)
Study Title: "Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (5 mg/1000 mg) compared with the free combination of linagliptin and metformin extended release tablets in healthy subjects (an openlabel, randomised, single dose, two-way crossover trial)"

Sample Analysis: From July 26 to August 11, 2014

Study#3: 1288-0011 (1288.11)
Study Title: "Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (2.5 mg/1000 mg) compared with the free combination of linagliptin and metformin extended release tablets in healthy subjects (an open-label, randomised, single dose, two-way crossover trial)"

Sample Analysis: From July 09 to July 26, 2014

Bioanalytical Site:

(b) (4)

OSIS scientists, Xikui Chen, Ph.D. and Paul Yeh, Ph.D. conducted the inspection of the bioanalytical portion of the studies from (b) (4). The audit covered the bioanalytical method

validation and sample analysis of linagliptin. The audit also included a thorough review of facilities and equipment, review of study records and correspondence, and interviews and discussions with (b) (4) management and staff. As a global assessment of the firm's bioanalytical operations, several key study components were selected for audit to represent the firm's bioanalytical operations since the previous inspection.

At the conclusion of the inspections, a one-item Form FDA 483 was issued at (b) (4). At the time of writing this review, the firm's response to Form FDA 483 has not been received. Our evaluation of the observation is discussed below.

Study 1288.9 (b) (4):

- 1. Failure to record plasma sample movements in Nautilus sample tracking system from -20°C freezer to a room temperature storage for Subjects 133, 138, 139, 140, 141, 146, 147, 148, 149, 150, 152, 208, 209, 210, 211, 212, 213, 214, and 215 in run 20 for study 1288.9.**

OSIS Evaluation:

Run 20 of study 1288.9 included 151 study samples for Subjects 133, 138, 139, 140, 141, 146, 147, 148, 149, 150, 152, 208, 209, 210, 211, 212, 213, 214, and 215. We currently don't know the sample movement for run 20 and therefore, the conditions under which the samples were handled. Thus, we recommend not accepting run 20. All the other data in Study 1288.9 are acceptable.

A total of 2261 study samples were analyzed in study 1288.9. Because the samples in run 20 make up only 6.68% of the total samples, excluding run 20 is unlikely to have an impact on the overall study outcome.

Recommendations:

Following review of the EIR and the inspectional finding, the data generated for study 1288.009 were found to be reliable. Therefore, we recommend that the data for the bioanalytical portion of the audited studies (b) (4) 1288-0009 (except run 20) and 1288-0011 be accepted for further agency review.

Li-Hong Yeh, Ph.D.
DNDBE, OSIS

Xikui Chen, Ph.D.
DGDBE, OSIS

Final Classification:

Analytical

VAI

CC:
OTS/OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller/Kadavil
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Cho/Yeh
OTS/OSIS/DGDBE/Haidar/Skelly/Choi/Chen

Draft: PY 01/27/2016
Edit: AD 02/06/2016; XC 02/11/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE
Program/Bioanalytical Sites/ (b) (4)

OSI fil (b) (4)
FACTS: (b) (4)

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Attachment 1: Application covered during the inspection.

NDA Number	FACTS	Location
2 6 Non Responsive	(b) (4)	(b) (4)

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/s/

LI-HONG P YEH
02/19/2016

CHARLES R BONAPACE
02/19/2016



Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

BIMO Inspection Assignment - General Information Section**FACTS: 11581819****Memorandum of NDA 208026 - Initiated clinical bioequivalence (BE) study Inspection Assignment**

Date: December 1, 2015

From: Sam H. Haidar, Ph.D., R.Ph.
Acting Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences
Center for Drug Evaluation and Research

To: Chief
Medical Products & Tobacco Trip Planning Branch
Division of Medical Products and Tobacco Inspections
Office of Medical Products and Tobacco Operations

Subject: **FY 2016, CDER High Priority Pre-Approval Data Validation Inspection,**
Bioresearch Monitoring, Human Drugs, CP 7348.001

Preannounce: No

Compliance Program: 7348.001
PAC Code: 48001A
Priority: High
Operation Code: 11 (Foreign inspection)
31 (Sample collection)

Application Number: NDA 208026
Product Name: Linagliptin/Metformin extended release (fixed dose combination)]

Sponsor: Boehringer Ingelheim, CT, USA
Protocol Number: 1288.0009; 1288.0011

Inspection Due Date: To be determined
EIR Due Date: March 22, 2016

Center Participation: No.
Joint Regulatory Agency Participation: No

Establishment(s) for inspection	FEI Number	FACTS Number
Boehringer Ingelheim Pharma GmbH & Co. KG Human Pharmacology Centre / Department of Translational Medicine Birkendorfer Str. 65,	Refer to ORA	FACTS: 11581819

Biberach/Riss, Germany

Note

Prior to the beginning of the inspection, please contact:

Xingfang Li M.D., RAC
Office of Scientific Investigations
Room 5219, HFD-45
10903 New Hampshire Ave.
Building 51, White Oak
Silver Spring, MD 20993
Tel:301-796-7368

To verify the focus and intent of the inspection. We frequently receive real-time information from the review team that may change the focus of the inspection.

Please follow the compliance program (7348.001) with emphasis on the specific instructions in this memorandum.

If significant deviations are found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data, we request that you expand the scope of your inspection as necessary and contact me immediately.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the OSIS POC.

OSIS POC:

Arindam Dasgupta, Ph.D.
Lead Pharmacologist
Office of Study Integrity and Surveillance
Tel: 1-301-796-3326
Fax: 1-301-847-8748
E-mail: arindam.dasgupta@fda.hhs.gov

At the end of the inspection, send an e-mail to CDER-OSIS-BEQ@fda.hhs.gov with any inspection findings. If a form FDA-483 is issued, send e-mail to CDER-OSIS-BEQ@fda.hhs.gov. Forward the EIR and exhibits to the Center contact address the following:

If electronic: CDER-OSIS-BEQ@fda.hhs.gov

If paper: Ms. Dinah Miller
FDA/CDER/OTS/OSIS
WO51 RM5333 HFD-45
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Important: forward any post-inspection correspondence from the establishment as soon as possible. All post-inspection correspondence must be reviewed prior to issuing any post-inspection notification of compliance status.

Background information

ECMS link (background information and inspection memo)	http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f880c0df77
Study # 1	1288.09 Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (5 mg/1000 mg) compared with the free combination of linagliptin and metformin extended release tablets in healthy subjects (an open-label, randomised, single dose, two way crossover trial)
Study # 2	1288.11 Bioequivalence of a fixed dose combination tablet of linagliptin/metformin extended release (2.5 mg/1000 mg) compared with the free combination of linagliptin and metformin extended release tablets in healthy subjects (an open-label, randomised, single dose, two way crossover trial)
Planned # of Sites	1
Investigator for 1288.09	Dr Fabian Müller Boehringer Ingelheim Pharma GmbH & Co. KG Department of Translational Medicine and Clinical Pharmacology, Human Pharmacology Centre Birkendorfer Str. 65 88397 Biberach/Riss, Germany
Investigator for 1288.11	Tobias Brand Boehringer Ingelheim Pharma GmbH & Co. KG Department of Translational Medicine & Clinical Pharmacology Human Pharmacology Centre Birkendorfer Straße 65 88397 Biberach an der Riß Germany Phone: +49 (0)7351 54-94861 Fax: +49 (0)7351 54-2181
Instructions for collecting a list of BE studies at the site in the last 5 years	Please collect a list of bioequivalence studies performed at the site in the last 5 years. The list should include information on test and reference reserve samples retained at the site or at a third party for the bioequivalence studies. Please refer to Table 1 for an example.
Additional instructions to the ORA Investigator	In addition to the compliance program elements, other study specific instructions may be provided by the OSIS POC prior to the inspection. Therefore, we request that the OSIS POC be contacted for further instructions before the inspection, and also regarding data anomalies or questions noted during review of study records. The ORA investigator should contact the OSIS POC for inspection-related questions or clarifications.

Specific instructions for Reserve Samples and Clinical Data Audit

RESERVE SAMPLES

Because these bioequivalence studies are subject to 21 CFR 320.38 and 320.63, the site conducting the studies is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the applicant for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically

addresses **the requirements for bioequivalence studies**
(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples
(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

Please follow the instructions below:

- ☐ Verify that reserve samples were retained according to the regulations.
- ☐ If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager, and that the sponsor was notified in writing of the location. In an event the reserve samples were not retained or are not adequate in quantity, please notify the POC immediately.
- ☐ Please obtain a written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a, Affidavit.
- ☐ Samples of the test and reference products **in their original containers** should be collected and shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening, at the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: (314) 539-2135

CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

- ☐ Confirm that informed consent was obtained for all subjects enrolled at the site.
- ☐ Audit the study records for all subjects enrolled in both studies.
- ☐ Compare the study report submitted to FDA with the original documents at the site.
- ☐ Check for under-reporting of adverse events (AEs).
- ☐ Check for evidence of inaccuracy in the electronic data capture system.
- ☐ Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection: _____

FACTS: **11581819**

- ☐ Number of subjects screened at the site: _____
- ☐ Number of subjects enrolled at the site: _____
- ☐ Number of subjects completing the study: _____
- ☐ Verify from source documents that evaluations related to the primary endpoint were accurately reported in the study report.
- ☐ Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- ☐ Confirm that site personnel followed SOPs during study conduct.
- ☐ Examine correspondence files for any applicant or monitor requested changes to study data or reports.
- ☐ Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- ☐ Other Comments:

Email cc:

ORAHQ/OMPTO/DMPTI
OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller
OSIS/DNDBE/Bonapace/Dasgupta/Cho
OSIS/DGDBE/Haidar/Skelly/Choi/Li

Draft: XFL 11/19/2015

Edit: MFS 11/19/2015; SHH 12/1/2015

ECMS: [Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance](#)/INSPECTIONS/BE Program/Clinical Sites/Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

BE File#: 6998

FACTS: 11581819

Table 1

SL NO.	Study number	Drug Name	Fast/Fed	Sponsor	Submission	Study Conduct Dates	Reserve Samples	Quantity	Lot# for Test and Reference
1	XXXXX	Aspirin + Dipyridamole Capsules	Fast	XXXX	USFDA	(b) (4)	At Site	300 for test, 200 for reference	XXXX and XXX
2	XXXXX	Montelukast	Fed	XXXXX	unknown	XXXXX	Third Party	two kits	XXXX and XXX
3	XXXXX	XXXXXXXX	Fast	XXXXXX	Pilot	XXXXX	Not retained	two bottle for test, two bottles for reference	XXXX and XXX

Xingfang Li -S

Digitally signed by Xingfang Li -S
 DN: c=US, o=U.S. Government, ou=HHS,
 ou=FDA, ou=People, cn=Xingfang Li -S,
 0.9.2342.19200300.100.1.1=2000576511
 Date: 2015.12.02 23:01:13 -05'00'

Xingfang Li, MD, RAC
 Consumer Safety Officer
 Division of Generic Drug Bioequivalence Evaluation (DGDBE)
 Office of Study Integrity and Surveillance (OSIS)

Sam H. Haidar, Ph.D., R.Ph.
 Acting Director
 Division of Generic Drug Bioequivalence Evaluation
 Office of Study Integrity and Surveillance (OSIS)

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/s/

XINGFANG LI
12/09/2015

SAM H HAIDAR
12/09/2015

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Application: [NDA 208026](#)

Application Type: [New NDA](#)

Name of Drug/Dosage Form: [Jentadueto XR \(linagliptin and metformin hydrochloride extended-release\) tablets](#)

Applicant: [Boehringer Ingelheim Pharmaceuticals, Inc.](#)

Receipt Date: July 27, 2015

Goal Date: May 27, 2016

1. Regulatory History and Applicant's Main Proposals

[This is a 505 \(b\)\(1\) New Drug Application \(NDA 208026\) for linagliptin and metformin hydrochloride extended-release fixed dose combination \(FDC\) tablets for once-daily administration in patients with type 2 diabetes mellitus](#)

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI) submitted June 22, 2015. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment: *Waiver was requested*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: Add trade name

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “To report **SUSPECTED ADVERSE REACTIONS**, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “See 17 for **PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “See 17 for **PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “See 17 for **PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

N/A

Selected Requirements of Prescribing Information

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD E WHITEHEAD
09/15/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208026	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Jentaducto XR Established/Proper Name: linagliptin and metformin HCl extended-release Dosage Form: tablets Strengths: 2.5mg/1000mg, 5mg/1000mg		
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. Agent for Applicant (if applicable): NA		
Date of Application: July 27, 2015 Date of Receipt: July 27, 2015 Date clock started after UN: NA		
PDUFA Goal Date: May 27, 2016		Action Goal Date (if different): May 27, 2016
Filing Date: September 25, 2015		Date of Filing Meeting: September 9, 2015
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	☐ 351(a) ☐ 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	☒ Standard ☐ Priority
<i>The application will be a priority review if:</i> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted	☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): (b) (4)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	☒	☐		

to the supporting IND(s) if not already entered into tracking system.					
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>		☒	☐	☐	
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		☐	☒		
If yes, explain in comment column.					
If affected by AIP, has OC been notified of the submission? If yes, date notified:		☐	☐		
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?		☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application (check daily email from UserFeeAR@fda.hhs.gov): ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (Check the 356h form,		☐	☒		Data required for

cover letter, and annotated labeling). If yes , answer the bulleted questions below:				review are incorporated by reference from NDAs 201280 (linagliptin), 201281 (linagliptin/metformin FDC), and right of reference to NDA 021748 (metformin XR).																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒																		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☒																		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	☐	☒																		
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													☒	☐		Other listed drug held by applicant therefore all patents and exclusivities belong to applicant
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i> <table border="1"> <thead> <tr> <th>Exclusivity</th> <th>YES</th> <th>NO</th> <th>NA</th> <th>Comment</th> </tr> </thead> <tbody> <tr> <td>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</td> <td>☐</td> <td>☒</td> <td></td> <td></td> </tr> <tr> <td>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</td> <td>☐</td> <td>☐</td> <td>☒</td> <td></td> </tr> </tbody> </table> <i>If yes, consult the Director, Division of Regulatory Policy II,</i>					Exclusivity	YES	NO	NA	Comment	Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	☐	☒			If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	☐	☐	☒		
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	☐	☒																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	☐	☐	☒																	

Office of Regulatory Policy				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☐	☒	☐	No request in application
If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic)			
	☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹	☒	☐	☐	

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

If not, explain (e.g., waiver granted).				
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☐	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies</i>	☐	☒		No FDA3454 or signatures provided, however a table with investigators provided noting all investigators listed are employees of BI

that are the basis for approval.				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	☒	☐	☐	
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?	☐	☐	☒	
<i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>				
<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?	☐	☐	☒	
<i>If yes, date consult sent to the Controlled Substance Staff:</i>				
For non-NMEs: Date of consult sent to Controlled Substance Staff:				
Pediatrics	YES	NO	NA	Comment
<u>PREA</u>				
Does the application trigger PREA?	☒	☐		
<i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>				

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?	☒	☐	☐	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	☒	☐	☐	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	☐	☒		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	☒	☐	☐	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	☐	☒	☐	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

<i>If no, request applicant to submit SPL before the filing date.</i>	☒	☐	☐	
Is the PI submitted in PLR format? ⁴	☒	☐	☐	
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	☒	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☒	☐	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒	Not Applicable		
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☐	☐	☐	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	Pediatric & Maternal Health Consult Requested to review PLLR labeling
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	☐	☒		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): January 6, 2015	☒	☐		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	☐	☒		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 9, 2015

BACKGROUND: Boehringer Ingelheim (BI) is submitting an application for the fixed-dose combination (FDC) of linagliptin and metformin hydrochloride extended-release (XR) for the treatment of adults with type 2 diabetes mellitus. The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes in whom treatment with both linagliptin and metformin hydrochloride is appropriate. Linagliptin is a selective, orally-administered, xanthine-based dipeptidyl-peptidase-4 (DPP-4) inhibitor. Linagliptin received its first worldwide marketing approval in the US on May 2, 2011 and is marketed as Tradjenta (linagliptin) tablets. The fixed-dose combination of linagliptin and metformin immediate-release (IR) has been approved in the US (on Jan 30, 2012). It is marketed as Jentadueto (linagliptin and metformin hydrochloride) tablets.

This clinical development program was designed to bridge the existing clinical efficacy and safety data (from Tradjenta and Jentadueto clinical trials) by demonstrating bioequivalence of the FDC tablets to the free combinations of the individual components co-administered in healthy men and women in phase I studies.

On October 11, 2011, and June 26, 2013, the Division provided written responses to the meeting requests BI submitted. Agreements on the “phase I only” clinical program were reached in these interactions. Briefly, in vivo bioequivalence should be shown for all tablet strengths under fed and fasted conditions. If bioequivalence for a tablet strength could be established after single-dose administration, bioequivalence after multiple-dose administration would not be necessary. The Division also agreed to the use of Glumetza 500 mg as a reference product for the bioequivalence studies, since the linagliptin/metformin XR FDC formulations are based on the same system used in Glumetza 500 mg.

On January 6, 2015, the Division provided written responses to the questions posed in the pre-NDA meeting package. On March 4, 2015, the Division sent additional comments on the plan for the 4-month safety update. Agreements were reached on the proposed content and format of the Modules 2 to 5 of the NDA, the electronic submission plan, and the proposed content of the 4-month safety update. Regarding the clinical documents in the NDA, the Division agreed to BI’s proposal of cross-referencing the existing clinical safety and efficacy data for linagliptin (Tradjenta; NDA 201280), the combination of linagliptin/metformin IR (Jentadueto; NDA 201281), and metformin XR (Glumetza; NDA 021748). The Division requested case report forms and narratives for all subjects who discontinued from the phase I studies due to adverse events or who had serious adverse events (regardless of discontinuation or not). The Division agreed to BI’s proposal that clinical summaries (Module 2.7) or integrated summaries (ISE/ISS) are not required as only phase I studies have been conducted for this NDA. However, the Division requested a clinical overview (Module 2.5) to “discuss how the cross referenced clinical data was used to support this new drug product, present an overview of clinical data, and any other relevant clinical summary in order to facilitate an efficient review by the Division.” The division agrees that a 4-month safety update will be prepared using any relevant post-marketing data and medical literature data similar to the searches performed for Jentadueto periodic benefit risk evaluation report (PBRER), which is also provided with this submission. BI has proposed to provide narratives (CIOMS report format) of any cases which are included in the discussion.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Richard Whitehead	Y
	CPMS/TL:	Pam Lucarelli	Y
Cross-Discipline Team Leader (CDTL)	Lisa Yanoff		Y
Division Director/Deputy	Jean Marc Guettier		N
Office Director/Deputy	NA		
Clinical	Reviewer:	Hyon Kwon	Y
	TL:	Lisa Yanoff	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:	NA	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:	NA	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NA	
	TL:	NA	
Clinical Pharmacology	Reviewer:	Sang Chung	Y
	TL:	Manoj Khurana	Y
• Genomics	Reviewer:	NA	
• Pharmacometrics	Reviewer:	NA	
Biostatistics	Reviewer:	Jiwei He	Y
	TL:	Mark Rothmann	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	David Carlson	Y
	TL:	Todd Bouncier	N
No comments for 74 day letter			
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC) Review Team:	ATL:	Su Tran	Y
Comments for 74 day letter	RBPM:	Anika Lalmansingh	N
• Drug Substance	Reviewer:	NA	
• Drug Product	Reviewer:	NA	
• Process	Reviewer:	NA	
• Microbiology	Reviewer:	NA	
• Facility	Reviewer:	NA	
• Biopharmaceutics	Reviewer:	Albert Cheng	Y
• Immunogenicity	Reviewer:	NA	
• Labeling (BLAs only)	Reviewer:	NA	
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Sharon Williams	Y
	TL:	Melissa Hulett	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Charuni Shah	Y
	TL:	NA	
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Mishale Mistry	Y
	TL:	NA	
OSE/DRISK (REMS)	Reviewer:	NA	
	TL:	NA	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	
	TL:	NA	

Bioresearch Monitoring (OSI)	Reviewer:	NA	
	TL:	NA	
Controlled Substance Staff (CSS)	Reviewer:	NA	
	TL:	NA	
Other reviewers/disciplines			
PMHS Comments sent as IR on August 07, 2015	Reviewer:	Miriam Diatale	Y
	TL:	Linda Lewis	N
Other attendees			

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments

CLINICAL Comments: comment reflected in 74 day letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no , explain: Clinical Pharmacology BE studies	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments: Request Electronic data for Study 1288.10. Electronic data for the final BE analysis format (i.e., Subject ID, Period, Sequence, Treatment/Formulation, Meal Condition, AUC and Cmax) – all studies	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: comment reflected in 74 day letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO

<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) - Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? - If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
What late submission components, if any, arrived after 30 days?	
Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO
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REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Jean Marc Guettier Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments: PDUFA Goal Date: May 27, 2016 Stamp Date: July 27, 2015 Filing Date: September 25, 2015 Day 74 Letter Date: October 9, 2015 Mid-cycle Review- December 16, 2015, 1-2PM Wrap-up Meeting- April 20, 2016, 10-11AM Primary Review Completion Goal Date: April 22, 2016 Send labeling/PMR/PMC/REMS to applicant: ~April 29, 2016 Secondary Review Completion Goal Date: April 29, 2016	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74

☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRA's completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD E WHITEHEAD
09/15/2015