CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-024

CHEMISTRY REVIEW(S)

ActoPlus MET™ XR
(pioglitazone HCl/metformin HCl extended release)
Tablets
NDA 22-024

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Takeda Global Research & Development Center, Inc.
475 Half Day Road
Lincolnshire, IL 60069

Indication: Adjunct to diet and exercise as a once daily, fixed dose, combination therapy to improve glycemic control in patients with type 2 diabetes mellitus.

Presentation: The drug product is supplied in two strengths, either 15 mg pioglitazone/1000 mg metformin or 30 mg pioglitazone/1000 mg metformin, as extended release tablets and is packaged in 30, 60, and 90-count HDPE bottles, with desiccant, as market packages or (b) (4) as physician samples.

EER Status: **Withold** 18-Jul-2006

Consults: Pharm/Tox – Acceptable (cf. NDA 21-073 and 21-574)
ClinPharm - Acceptable 4-Jan-2007
Methods Validation – Method validation package is provided. Samples will be requested for method validation study to be conducted by FDA laboratories.
EA – Categorical exclusion granted under 21 CFR §25.31(a) for both drugs
DMETS – Acceptable 8-JAN-2007

Original Submission: 31-Mar-2006
Amendments: 03-Nov-2006
30-Nov-2006

Post-Approval Agreements: None

Drug Substances:

Pioglitazone HCl

Pioglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). Activation of PPARγ nuclear receptors regulates the transcription of insulin-related genes involved in the control of glucose production, transport, and utilization. Pioglitazone HCl has a chemical name of (±)-5-[[4-[2-(5-Ethyl-2- pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione hydrochloride, a molecular formula of $C_{19}H_{20}N_2O_3S \cdot HCl$, and molecular weight of 392.90 g/mole. The hydrochloride salt is a white crystalline

powder that is soluble in (b) (4) and slightly soluble in ethanol. Water solubility is pH dependent and is <0.01 mg/mL at physiological pH. The drug molecule is chiral and the racemate is used in the formulation. The drug substance, pioglitazone HCl, is that approved for use in NDA 21-073 for Takeda's Acto® tablets and reference is made to such and its supplements for all chemistry, manufacturing, and controls information pertaining to pioglitazone HCl.

The release specifications include appearance, identity, assay, related impurities, heavy metals, residual solvents, moisture content, and particle size distribution. The proposed regulatory methods have been validated. The reference standard, a (b) (4) commercial lot, has been developed, characterized, and purity data provided.

Bulk pioglitazone HCl, packed in (b) (4) inside a (b) (4) is stable for up to 4 years when stored at room temperature (25°C/60 %RH) or up to 6 months when stored at elevated temperature (40°C/75%RH).

Metformin HCl

Metformin is a biguanide class of antihiperglycemic agent that acts primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconcogenesis. Metformin HCl has a chemical name of 1,1-Dimethylbiguanide hydrochloride, a molecular formula of $C_4H_{11}N_5 \bullet HCl$, and a molecular weight of 165.62 g/mole.

CMC information on the drug substance, metformin HCl, is described in the Type II DMF (b) (4) detailed information on manufacture, in-process controls, analytical procedures and their validation, and stability is included. The applicant has summarized information regarding nomenclature, general properties, manufacturing sites, acceptance specifications, reference standard, batch analysis data, structural elucidation, and stability studies in the NDA.

The release specifications include description, identification, loss on drying, residue on ignition, heavy metal, assay, related impurities, residual solvents and particle size. These specifications comply with the USP monograph for metformin hydrochloride. The drug substance specification differs from the USP monograph in (b) (4). The reference standard for metformin HCl is commercially available from USP.

Bulk metformin HCl, packed in (b) (4) inside a (b) (4), is stable for up to 5 years at room temperature (25°C/60% RH) or at elevated temperature (40°C/75% RH).

Conclusion: Drug substance information is acceptable.

Drug Product:

The drug product is a fixed dose combination tablet, composed of a metformin HCl extended release core that is coated with an immediate release pioglitazone HCl formulation, and is available as two strengths with the following description:

> The 15/1000 tablets contain 15 mg pioglitazone /1000 metformin mg, are white to off-white film-coated, round tablets imprinted with "4833X" and "15/1000" in red on one side, and weigh 1255 mg.
>
> The 30/1000 tablets contain 30 mg pioglitazone /1000 metformin mg, are white to off-white film-coated, round tablets imprinted with "4833X" and "30/1000" in light blue on one side, and weigh 1291 mg.

Manufacture of the drug product utilizes Andrx's propriety Single Composition Osmotic Tablet (SCOT) delivery technology which, in this case, consists of a metformin HCl extended-release core that is coated with an immediate-release pioglitazone HCl formulation.

(b) (4)

The specification for the drug product includes description, identification (HPLC, TLC), assay (HPLC), content uniformity, drug release (dissolution), loss on drying, and related compounds. The proposed regulatory methods have been validated. The drug product reference materials are the same as those used for pioglitazone HCL and metformin HCL drug substances.

Stability data indicate that there are no significant changes in terms of description, assay, related compounds, dissolution, loss on drying, and microbial limits when tablets are stored under either long-term (25°C/60%) or accelerated (40°C/75%RH) conditions in HDPE bottles with closure and desiccant pack and in (b) (4). Photostability studies indicate no significant changes for known pioglitazone impurities and metformin impurities. However, pioglitazone unknown impurities increased slightly upon exposure to light. At high temperature and low humidity, all results met specification.

Based on 12 months of stability data for tablets packaged in HDPE bottles and blister packages stored under long-term and accelerated conditions, the requested expiration dating period of 24 months is acceptable.

Conclusion: Drug product information is acceptable.

Additional Items:

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

The applicant agrees to place one batch annually in the post-approval stability program.

A satisfactory response to the CMC labeling comments is pending. Strengths for Pioglitazone as free base and metformin as free base appear on label; label strengths should agree with the established names pioglitazone HCl and metformin HCl.

Overall Conclusion:

From a CMC perspective, the application is **Approvable** because of **Withold** recommendation from Office of Compliance.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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