CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-044

CHEMISTRY REVIEW(S)

Janumet™
(Sitagliptin Phosphate (+) Metformin Hydrochloride)
Tablets
NDA 22-044

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

Applicant: Merck & Co., Inc.
UG2CD-48
PO Box 1000
North Wales, PA 19454-1099

Indication: Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

Presentation: The drug product is supplied in two strengths (50 mg sitagliptin/500 mg metformin hydrochloride or 50 mg sitagliptin/1000 mg metformin hydrochloride) as immediate release film-coated tablets packaged in —— bottles (60, 180 and 1000-count) and in unit dose —— blister packages (50 count as 10-unit doses per foil).

EER Status: Acceptable 24-Jan-2007

Consults: Methods Validation – Agency revalidation not recommended.
EA – Categorical exclusion granted under 21 CFR §25.31(b) for both drugs.
Labeling – Under review (multi disciplinary approach).

Original Submission: 31-May-2006

Amendments: 24-Jul-2006
05-Jan-2007
05-Feb-2007
05-Feb-2007

Post-Approval Agreements: None

Drug Substances:

Sitagliptin Phosphate Monohydrate

Sitagliptin is a highly selective and potent inhibitor of the enzyme dipeptidyl peptidase 4 (DPP-4). DPP-4 inhibitors act by enhancing the levels of active incretin hormones. Sitagliptin is synthesized and present in the drug product as its phosphate

— monohydrate. Sitagliptin phosphate monohydrate has a chemical name is 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-[3-trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate, a molecular formula of $C_{16}H_{15}F_6N_5O \cdot H_3O_4P \cdot H_2O$, and a molecular weight of 523.32 g/mole. Sitagliptin phosphate monohydrate is a white to off-white solid, melting point ——— °C, and a pKa of — According to the Biopharmaceutics classification system (BCS) sitagliptin is a Class III (high solubility, low permeability)/borderline Class I (high solubility, high permeability) drug. Sitagliptin phosphate monohydrate is the drug substance of Januvia™ Tablets, which is described in and referred to Merck's approved NDA 21-995.

The release specifications include appearance, identity, assay, related impurities, moisture content, particle size distribution, residual metals, and chiral purity. The proposed regulatory methods have been validated. Residual metals and enantiomeric purity will be tested in-process only. However the criteria are retained in the specification. Based on development, no testing is performed for Polymorphic Form and Solvent ——— Content. The reference standard, a re-purified commercial lot, has been developed, characterized, and purity data provided.

Bulk sitagliptin phosphate monohydrate, packed in ——— is stable for long-term up to — years when stored at room temperature (25 °C/60 % RH).

Metformin HCl

Metformin is a biguanide class of antihiperglycemic agent that acts primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. Metformin HCl has a chemical name of 1,1-Dimethylbiguanide hydrochloride, a molecular formula of $C_4H_{11}N_5 \cdot HCl$, and a molecular weight of 165.62 g/mole. Metformin is a class 3 (high solubility, low permeability) BCS drug.

CMC information on the drug substance, metformin HCl, is described in the Type II DMF ———; detailed information on its characterization, manufacture, in-process controls, analytical procedures and their validation, and stability is included.

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 (1) additional particle size criteria and (2) more stringent limits on impurities. The reference standard for metformin HCl is commercially available from USP.

Bulk metformin HCl, packed in ———, is stable long-term up to —years at room temperature (25 °C/60 % RH).

Conclusion: Drug substance information is acceptable.

Drug Product:

The drug product is a fixed dose combination tablet, composed of a fixed dose of sitagliptin and a variable dose of metformin hydrochloride, and is available as two strengths with the following description:

- The 50/500 tablets contain 50 mg sitagliptin free base /500 mg metformin HCl, are light pink film-coated, oblong (17.3 mm x 8.4 mm) biconvex tablets debossed "575" on one side, blank on the other, and weigh 706.2 mg.

- The 50/1000 tablets contain 50 mg sitagliptin free base /1000 mg metformin HCl, are red film-coated, oblong (21.2 mm x 10.3 mm) biconvex tablets debossed "577" on one side, blank on the other, and weigh 1333 mg.

Each film-coated tablet of Janumet™ contains the following inactive ingredients: microcrystalline cellulose ———, polyvinylpyrrolidone ———, sodium lauryl sulfate ———, and sodium stearyl fumarate ———. The film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and black iron oxide. All excipients, including film coating components, meet compendial requirements.

The manufacturing process includes

The specification for the drug product includes appearance, identification (————), assay, degradation products (individual unspecified and total degradation products), dissolution (both actives are measured in the same media by the same HPLC method), and uniformity of dosage units (mass and active content). The proposed regulatory methods have been validated. The drug product reference materials are the same as those used for sitagliptin phosphate monohydrate and metformin hydrochloride drug substances.

Stability data indicate that there are no significant changes in terms of appearance, assay, related compounds, dissolution, disintegration, hardness and moisture, when tablets are stored at either 25 °C/60 % RH or at 30 °C/65 % RH in ——— bottles with closure and in ——— blister packages. Photostability studies indicate that the tablets are stable when exposed to light.

Based on 12 months of stability data at either 25 °C/60 % RH or 30 °C/65 % RH for tablets packaged in ——— bottles and blister packages, and 6 months at 40 °C/75 % RH, the requested expiration dating period of ———— is acceptable under the proposed storage conditions: "Store at 20 – 25 °C (68 – 77 °F); excursion permitted to 15 – 30 °C (59 – 86 °F) [see USP Controlled Room Temperature]."

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 at least one batch of each strength annually in the post-approval stability program.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval**, pending agreement on product labeling.

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

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