ABBOTT

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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

RE: **Citizen's Petition for ANDA Suitability**

Ondansetron Hydrochloride Injection
Ondansetron Hydrochloride Injection Premixed

In accordance with 21 CFR 10.20, in the format specified in 21 CFR 10.30, and containing information required by 21 CFR 314.93, the undersigned submits this petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act to obtain permission from the Commissioner of Food and Drugs to submit abbreviated applications for a new drug whose route of administration, dosage form, or strength differ from that of a listed drug.

Action Requested

The petitioner requests that the Commissioner permits abbreviated new drug applications (ANDAs) to be filed for Ondansetron Hydrochloride Injection (4 mg/2 mL and 8 mg/4 mL prefilled syringes) and Ondansetron Hydrochloride Injection Premixed (8, 12, 16, 20 and 24 mg in 50 mL 5% Dextrose Injection).

The listed drugs, Zofran® (ondansetron hydrochloride) Injection and Injection Premixed, manufactured by GlaxoSmithKline, are available in three dosage forms:

(1) 4 mg/2 mL single-dose vial
(2) 40 mg/20 mL multidose vial
(3) Premixed, 32 mg/50 mL, in 5% Dextrose (no preservatives) single-dose, flexible plastic container

A copy of the approved labeling for the listed drug Zofran® is provided as **Exhibit I.**

The variations requested in this petition are to allow seven additional dosage forms:

(1) **4 mg/2 mL prefilled syringe**
(2) **8 mg/4 mL prefilled syringe**
(3) Premixed, **8 mg**/50 mL, in 5% Dextrose (no preservatives) single-dose, flexible plastic container
(4) Premixed, **12 mg**/50 mL, in 5% Dextrose (no preservatives) single-dose, flexible plastic container
(5) Premixed, **16 mg**/50 mL, in 5% Dextrose (no preservatives) single-dose, flexible plastic container
(6) Premixed, **20 mg**/50 mL, in 5% Dextrose (no preservatives) single-dose, flexible plastic container
(7) Premixed, **24 mg**/50 mL, in 5% Dextrose (no preservatives) single-dose, flexible plastic container

The active ingredient (ondansetron hydrochloride) of the proposed drug products is of the same pharmacological or therapeutic class as that of the reference listed drug (Zofran®). The proposed drug products can be expected to have the same therapeutic effect as the reference listed drugs when administered to patients for each condition of use in the reference listed drug's labeling for which the applicant seeks approval.

A copy of the proposed labeling for the drug products that are the subject of this petition is provided as **Exhibit II**.

Statement of Grounds

I. Background

Ondansetron HCl injection is a selective 5-HT_3 receptor antagonist. It is indicated for:

(1) Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy including high dose cisplatin. Efficacy of the 32 mg single dose beyond 24 hours in these patients has not been established.
(2) Prevention of postoperative nausea and vomiting.

GlaxoSmithKline markets the injection as a 32 mg/50 mL premix in 5% Dextrose Injection and as a 2 mg/mL concentration in a 2 mL single dose vial and in a 20 mL multi-dose vial.

For the prevention of chemotherapy induced nausea and vomiting, the recommended adult IV dosage is a single 32 mg dose administered 30 minutes before the start of chemotherapy or three 0.15 mg/kg doses (30 minutes before chemotherapy, then 4 and 8 hours after the first ondansetron dose).

For postoperative nausea and vomiting, the recommended adult IV dosage is 4 mg before anesthesia induction or postoperatively[1].

II. Proposed Dosage Forms

Abbott Laboratories will file ANDAs for the currently marketed injectable dosage forms. The following additional dosage forms are also proposed:

4 mg/2 mL and 8 mg/4 mL prefilled syringes
8, 12, 16, 20 and 24 mg premixes in 50 mL 5% Dextrose Injection

III. Medical Rationale for Proposed Forms

Prefilled syringes eliminate the requirement for withdrawing doses from a vial. This minimizes preparation time, which is important when treating a condition that causes patient discomfort such as nausea and vomiting. The syringes are labeled throughout dose preparation and administration. This also reduces the risk of error from drawing an incorrect dose into a syringe. The 4 mg dose is anticipated to be used intravenously or intramuscularly. The Luer tip allows for direct intravenous administration through valved ports; a needle may be attached for intramuscular administration or injection through systems that require a needle for intravenous access.

A review of trials by Tramer et al[2], indicated that an 8 mg dose may also be used intravenously for post operative nausea and vomiting. Bernstein and Ong[3] determined that 8 mg ondansetron IV combined with dexamethasone was effective in controlling nausea and vomiting in patients receiving moderately and highly emetogenic chemotherapy. Alternative uses include compounding 8 mg admixtures for infusion over 15 minutes for patients weighing approximately 50 kg.

Ready to use premixed containers also reduce the risk of compounding error by providing a dosage form that comes labeled from the manufacturer. The clinician inserts an administration set and the drug is ready for infusion.

In head and neck cancer, an IV 24 mg ondansetron dose (165 cycles) was compared to 3 mg of IV granisetron (150 cycles) and 5 mg of tropisetron (148 cycles) for prevention of nausea and vomiting in chemotherapy naïve patients receiving cisplatin (80 to 100 mg/m^2)[4]. In this open labeled study, the ondansetron treated group demonstrated a complete response 73.3%, major response in 20.7%, minor response in 1.3% and failure in 4.7%.

Gebbia et al[5] studied 16 mg and 24 mg doses of IV ondansetron compared to 3 mg granisetron in the prevention of moderately emetogenic and highly emetogenic chemotherapy. Results indicated that both were effective for control of acute emesis with a lesser response for delayed emesis.

For patients weighing 75 kg, a 12 mg dose accommodates the 0.15 mg/kg prescription.

The range of premixed doses permits dosing flexibility if the patient experiences an adverse event related to the amount of drug. In his review[2], Tramer noted that the incidence of headache may be dose-related.

IV. Summary

The prefilled syringes offer a ready to use system for the clinician in doses that are used therapeutically.

Ready to use premixed infusions in the proposed concentrations give a range for the clinician to select based on the clinical condition of the patient and previous experience with ondansetron.

V. References

1. Prescribing Information. Zofran® (ondansetron hydrochloride) Injection and Injection Premixed. GlaxoSmithKline April 2002 (**Exhibit I**).
2. Tramer MR, Reynolds JM, Moore A, Henry J et al. Efficacy, dose response, and safety of ondansetron in prevention of postoperative nausea and vomiting. *Anesthesiology* 1997; 87:1277-1289 (**Exhibit III**).
3. Bernstein BJ and Ong C. Efficacy of a single 8 mg IV dose of ondansetron hydrochloride for preventing chemotherapy induced emesis. *Am J Health-Syst Pharm* 2002; 59: 650-652 (**Exhibit IV**).
4. Mantovani G, Maccio A, Bianchi A, Curreli L et al. Comparison of granisetron, ondansetron, and tropsetron in the prophylaxis of acute nausea and vomiting induced by cisplatin for the treatment of head and neck cancer: a randomized controlled trial. *Cancer* 1996; 77: 941-948 (**Exhibit V**).

5. Gebbia V, Cannata G, Testa A, Curto G et al. Ondansetron versus granisetron in the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 1994; 74: 1945-1952 (**Exhibit VI**).

Environmental Impact

We hereby request a categorical exclusion under 21 CFR 25.31(a). The proposed drug products will not be administered at higher dosage levels, for longer duration, or for different indications than that for the listed product. Approval of this petition will not increase the use of the active moiety.

Economic Impact

This information will be submitted if requested by the Commissioner.

Certification

As required by 21 CFR 10.30(b), certification that this petition is complete and contains all information both favorable and unfavorable, is provided as **Exhibit VII**.

We trust that the information presented in this Citizen's Petition is complete and shows our proposed products to be suitable for abbreviated new drug applications.

Sincerely,

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