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McDERMOTT, WILL & EMERY

October 22, 2001

Docket Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

# ANDA SUITABILITY PETITION

McDermott, Will & Emery submits this ANDA Suitability Petition under the provisions of section 505 (j)(2)(C) of the Federal Food, Drug and Cosmetic Act requesting that the Commissioner of Food and Drugs allow the submission and filing of an Abbreviated New Drug Application ("ANDA") for Ondansetron Hydrochloride Tablets, 16mg.

## A. Action Requested

The Petitioner requests that the Commissioner of Food and Drugs allow the submission and filing of an ANDA for Ondansetron Hydrochloride Tablets, 16mg, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act. The reference listed drug, Zofran® Tablets, marketed by GlaxoSmithKline under NDA 20-103, is available in 4mg, 8mg and 24mg tablets. The Petitioner is requesting permission to file

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an ANDA for an intermediate tablet strength of 16mg. A single-dose of 16mg of Ondansetron Hydrochloride is provided for in the approved labeling of the reference-listed drug Zofran®. The indication for this dose is post-operative nausea and vomiting. A review of current labeling and the literature indicates that a single dose of 16mg of Ondansetron is not a dose that would be a candidate for use in the pediatric patient population. A copy of the approved labeling for the reference listed drug is attached. Also enclosed with this petition are comparative dissolution data, summary bioequivalence data and a draft package insert for the proposed ANDA product.

## B. Statement of Grounds

### 1. A 16mg dose of Ondansetron Hydrochloride is provided for in the labeling of the Reference Listed Drug.

The reference listed drug, Zofran® Tablets, marketed by GlaxoSmithKline under NDA 20-103, is available in 4mg, 8mg and 24mg tablets. The DOSAGE AND ADMINISTRATION section of the package insert for Zofran® Tablets includes the following:

> **Post-operative Nausea and Vomiting:** The recommended dosage is 16mg given as two 8-mg Zofran® tablets or two 8-mg Zofran® ODT tablets or 20 mL (4 teaspoonfuls equivalent to 16mg of Ondansetron) of Zofran® Oral Solution 1 hour prior to the induction of anesthesia.

**Pediatric Use**: There is no experience with the use of Zofran® tablets, Zofran® ODT Tablets, or Zofran® Oral Solution in the prevention of post-operative nausea and vomiting in pediatric patients.

**Geriatric Use**: The dosage is the same as for the general population.

Thus, it is clear that the approved labeling for the reference-listed drug, Zofran®, provides for a single dose of 16mg of Ondansetron for use in adults for the indication of post-operative nausea and vomiting.

**2. A single dose of 16mg of Ondansetron HCl is not a dose that would be a candidate for use in the pediatric patient population for post-operative nausea and vomiting.**

The approved labeling for the reference listed drug states that there is no experience with the use of Zofran® tablets, Zofran® ODT Tablets, or Zofran® Oral Solution in the prevention of post-operative nausea and vomiting in pediatric patients. Notwithstanding, based upon a review of Dosage and Administration Section of the approved labeling regarding the dose of Ondansetron, the drug is approved for use in pediatric patients at one-half the adult dose for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, that is, the dose is 8mg twice a day for patients 12 years and older and 4mg three times a day for pediatric patients 4 to 11 years old. The recommended dose in adult patients for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy is a single 24mg dose. While not approved for pediatric use in this latter indication, review of the medical literature indicates

that a single oral dose of 16mg of Ondansetron is not a dose that would be a candidate for use in the pediatric patient population.

There are reports in the medical literature of an initial high dose intravenous injection of Ondansetron used in naïve pediatric oncology patients.[1,2] Sandoval *et al.*, concluded that the results of their study suggest that single high-dose Ondansetron is a practical alternative to multiple-standard dose therapy and cited less preparation time and facilitation of administration of inpatient and outpatient chemotherapy as reasons for use of this dosage regimen. Brock *et al.*, concluded that the results of their study showed that an increase in loading dose to $10mg/m^2$ (comparable to a maximum dose of 16mg) does not improve the control of vomiting or nausea in children receiving highly emetogenic chemotherapy. While there are such reports in the medical literature, these reports are not applicable to the request of the Petitioner because of the difference in dosage form (intravenous injection versus oral tablet) and the differences in indication for use (prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy in pediatrics versus prevention of post-operative nausea and vomiting in adults). Moreover, the results of the studies reported in the literature are equivocal in terms of use of high initial dosing of injectable Ondansetron in prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy in pediatrics.

In sum, based upon a review of the current approved package insert for the reference listed drug, Zofran® Tablets, and a review of the literature, the Petitioner

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[1] Sandoval, C., Corbi, D., *et al.*, "Randomized Double-Blind Comparison of Single High-Dose Ondansetron and Multiple Standard-Dose Ondansetron in Chemotherapy-Naïve Pediatric Oncology Patients", Cancer Investigations, 17(5) 309-313 (1999).

believes that single oral dose of 16mg of Ondansetron is not indicated for and should not be used in the pediatric patient population for post-operative nausea and vomiting.

### 3. Comparative Dissolution and Demonstration of Bioequivalence.

The ANDA applicant for the proposed product, Ondansetron Hydrochloride Tablets 16mg, is finalizing its formulation for all strengths of Ondansetron that it is intending to file ANDAs, *i.e.*, 4mg, 8mg and 24mg. The proposed formulation of the 16mg tablet would be compositionally proportional to the other strengths of the product which are under development. The ANDA applicant has conducted comparative dissolution studies on all strengths of its tablets (please note that the proposed 16mg tablets has been compared to 2 × 8mg of both the reference listed drug, Zofran® Tablets 8mg and the ANDA applicant's Ondansetron HCl tablets, 8mg). A summary of the currently available dissolution data are enclosed.

With regards to bioequivalence, the ANDA applicant intends to request a waiver of *in vivo* bioequivalence requirements for Ondansetron Hydrochloride Tablets, 16mg. The waiver will be based on comparative dissolution data, composition proportionality of the formulation and the *in vivo* bioequivalence studies that have been conducted on the ANDA applicant's Ondansetron Hydrochloride Tablets, 24mg. A summary of the *in vivo* bioequivalence studies conducted on the ANDA applicant's Ondansetron Hydrochloride Tablets, 24mg is enclosed.

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[2] Brock, P., Brichard, B., *et al.*, "An Increased Loading Dose of Ondansetron: a North European, Double-blind Randomised Study in Children, Comparing 5 mg/m$^2$ with 10mg/m$^2$", European Journal of Cancer, Vol. 32A, No. 10, 1744-1748 (1996).

## C. Conclusion

For the reasons identified above, Petitioner hereby requests that the Commissioner allow the submission and filing of an ANDA for Ondansetron Hydrochloride Tablets, 16mg.

## D. Environmental Impact

Petitioner believes that this petition does not require an environmental impact analysis report under 21 C.F.R. § 25.30(h).

## E. Economic Impact

An economic impact report is required only when requested by the Administration and such report has not been requested. 21 C.F.R. § 10.30(b).

## CERTIFICATION

Petitioner certifies that, to the best of its knowledge and belief, this Petition includes all of the information and views on which the Petition relies and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

Respectfully submitted,

David L. Rosen, R.Ph., J.D.