This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

# SCIENTIFIC DISCUSSION

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|---|---|
| **Name of the Finished Pharmaceutical Product** | [HA595 trade name][*] |
| **Manufacturer of Prequalified Product** | Cadila Pharmaceuticals Limited |
| **Active Pharmaceutical Ingredient(s) (API)** | Ondansetron hydrochloride dihydrate |
| **Pharmaco-therapeutic group (ATC Code)** | Serotonin (5-HT3) antagonists, ATC Code: A04AA01 |
| **Therapeutic indication** | [HA595 trade name] can be used in patients with HIV for:<br>• managing nausea and vomiting induced by cytotoxic chemotherapy in adults and in adolescents and children weighing at least 10 kg (body surface area at least 0.6 m2)<br>• managing nausea and vomiting induced by radiotherapy in adults<br>• preventing postoperative nausea and vomiting in adults |

## 1. Introduction

[HA595 trade name] can be used in patients with HIV for managing nausea and vomiting induced by cytotoxic chemotherapy, radiotherapy and preventing postoperative nausea and vomiting.

## 2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

### Active pharmaceutical Ingredient (API)

A CEP (Certificate of Suitability) issued by the EDQM was submitted for ondansetron hydrochloride dihydrate ensuring good manufacturing control and applicability of the respective Ph.Eur monograph to control the quality of the API.

### Other ingredients

Other ingredients used in the tablet formulation include lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, colloidal anhydrous silica and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains titanium dioxide, hypromellose and triacetin. Lactose monohydrate and magnesium stearate are from bovine and vegetable origin, respectively. TSE/BSE compliance declarations were provided for the excipients.

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

**Finished pharmaceutical product (FPP)**

*Pharmaceutical development and manufacture*

The multisource product is a white, oval, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablets are plain on both sides. The tablets are packaged in aluminium foil on aluminium foil blister cards.

Two strengths of ondansetron (as hydrochloride dihydrate) tablets proportionally similar in composition were developed: 4 mg and 8 mg. The development focused on the higher strength, which was used in the BE study against the WHO recommended comparator product Zofran (ondansetron hydrochloride dihydrate) 8 mg tablets. Once the formulation for the 8 mg strength was finalized, the 4 mg strength was pursued using dose-proportionality approach.

The aim of the formulation development strategy was to obtain a stable, robust multisource product bioequivalent to the WHO recommended comparator product. The selection of the excipients was based on the comparator product, API-excipient compatibility studies and their suitability to achieve the desired tablet characteristics. A wet granulation manufacturing process was selected due to the poor flow properties of the API. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics, including dissolution profile similarity with the comparator product. Satisfactory in-process controls have been established.

*Specifications*

The finished product specifications are pharmacopoeial based and include tests for description, identification of the API (IR), average weight, uniformity of weight, dissolution (HPLC detection), disintegration time, uniformity of dosage units (by content uniformity), related substances (TLC and HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

*Stability testing*

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with no significant changes or trends observed. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

**Conclusion**

The quality part of the dossier is accepted.

## 3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2011 according to internationally accepted guidelines.

A randomized, open-label, two-treatment, two-period, two-sequence, single dose, two-way crossover bioequivalence study of ondansetron hydrochloride 8 mg tablet (containing ondansetron hydrochloride dihydrate eq. to ondansetron 8 mg) of Cadila Pharmaceuticals Limited, India compared with Zofran® 8 mg tablets (containing ondansetron hydrochloride dihydrate eq. to ondansetron 8 mg) of GSK procured from Switzerland, in healthy, adult, human subjects under fasting condition (study no. 0211/006).

The objective of the study was to compare the bioavailability of the stated ondansetron hydrochloride dihydrate 8 mg tablet manufactured by/for Cadila Pharmaceuticals Limited, India (test drug) with the reference formulation Zofran® 8 mg tablet (GSK) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet ondansetron hydrochloride dihydrate 8 mg (ondansetron 8 mg)
Batch no. ET019E1001.

Treatment R: Reference – 1 tablet Zofran® 8 mg (ondansetron 8 mg)
Batch no. 9K002.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 18 samples within 24h post dose) were taken during each study period to obtain bioavailability characteristics AUC, $C_{max}$ and $t_{max}$ for bioequivalence evaluation. Drug concentrations for ondansetron were analysed using a validated LC-ESI-MS/MS method. The limit of quantification was stated to be about 1 ng/mL for ondansetron.

The study was performed with 26 participants; data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for ondansetron as well as statistical results are summarised in the following table:

**Ondansetron**

| **Pharmacokinetic Parameter** | **Test formulation (T)** arithmetic mean ± SD (geometric mean) | **Reference (R)** arithmetic mean ± SD (geometric mean) | **log-transformed parameters** | |
|---|---|---|---|---|
| | | | **Ratio** T/R (%) | **Conventional** 90% CI (ANOVAlog) |
| $t_{max}$ (h) | 1.70 ± 0.67 | 1.92 ± 0.72 | – | – |
| $C_{max}$ (ng/mL) | 35.9 ± 9.5 (34.7) | 40.3 ± 21.6 (36.6) | 94.7 | 87.1 – 102.9 |
| $AUC_{0-t}$ (ng·h/mL) | 226 ± 80 (212) | 249 ± 116 (229) | 92.9 | 84.5 – 102.1 |
| $AUC_{0-inf}$ (ng·h/mL) | 244 ± 87 (229) | 267 ± 119 (246) | 93.3 | 85.3 – 102.0 |

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and $C_{max}$ values regarding ondansetron. Accordingly, the test ondansetron hydrochloride dihydrate 8 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Zofran® 8 mg tablet (GSK).

A biowaiver was granted for the additional 4 mg tablet strength (Cadila Pharmaceuticals Limited, India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the ondansetron hydrochloride dihydrate 4 mg tablet was determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths was considered essential the same and the dissolution profiles between the formulations for the APIs were determined the same.

## 4. Summary of product safety and efficacy

[HA595 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [HA595 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. According to the submitted data on quality and bioavailability [HA595 trade name] is a direct scale down of [HA596 trade name]. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the

comparator product Zofran® 8 mg tablet (GSK) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA595 trade name]is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety

## 5. Benefit risk assessment and overall conclusion

### Quality

[Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [HA595 trade name] is used in accordance with the SmPC.

### Bioequivalence

[HA595 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

### Efficacy and Safety

Regarding clinical efficacy and safety, [HA595 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

### Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA595 trade name] was acceptable for the following indication: 'managing nausea and vomiting induced by cytotoxic chemotherapy, radiotherapy and preventing postoperative nausea and vomiting in HIV patients', and would allow inclusion of [HA595 trade name], manufactured at Cadila Pharmaceuticals Limited,1389, Trasad Road, Dholka Ahmedabad, Gujarat 382 225, India in the list of prequalified medicinal products.