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RESEARCH**

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MEDICAL REVIEW(S)

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CLINICAL REVIEW

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Established Name Ondansetron Hydrochloride
(Proposed) Trade Name Ondansetron Injection, USP
Therapeutic Class Antiemetic
Applicant Baxter Healthcare Corporation

Priority Designation Standard

Formulation Injection
Dosing Regimen 8 mg & 32 mg Single-dose
Indication Prevention of CINV
Intended Population Chemotherapy Patients

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**APPEARS THIS WAY
ON ORIGINAL**

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The approval of intravenous ondansetron hydrochloride of 32 mg I.V. single dose in a 0.9% saline diluent in 50 mL intravenous flexible plastic container is recommended by this Medical Reviewer for the following indication:

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

This single 32 mg dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. This is already an approved dose of ondansetron and the formulation is essentially the same as the 32 mg premixed Zofran® product currently marketed by GSK except for the use of saline instead of a dextrose vehicle. This dose is known to be safe for its intended use. To get approval, the sponsor should incorporate the labeling recommendations listed in the Medical Officer's Labeling Review and the NDA team's labeling recommendations. In addition, there should be no unexpired patent for the Zofran® 32 mg premixed injection at the time of approval of this NDA.

This medical reviewer *does not* recommend the approval of the proposed new lower single dose ondansetron 8 mg I.V. for the same above indication due to lack of substantial evidence of the effectiveness of this dose for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin in adult chemotherapy patients.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management steps are recommended.

1.2.2 Required Phase 4 Commitments

There are no Phase 4 commitments recommended.

1.2.3 Other Phase 4 Requests

There are no Phase 4 requests for this sNDA.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Zofran® (ondansetron hydrochloride), a selective 5-HT₃ antagonist, is an oral and parenteral antiemetic agent. It is the first selective serotonin blocking agent to be marketed and is currently approved for the prevention of chemotherapy, postoperative and radiotherapy induced nausea and vomiting. The injection form was originally approved for the prevention of chemotherapy induced nausea and vomiting (CINV) by the FDA on January 4, 1991 at a dose of 0.15 mg/kg x 3; and in 1993, a single 32 mg dose for the same indication was approved as an alternative to the multidose (0.15 mg/kg x 3 doses) regimen. The oral dosage forms (tablets, orally disintegrating tablets and oral solution) were subsequently approved for marketing as well as other antiemetic indications.

The applicant of this NDA, Baxter Healthcare Corporation, submitted a 505(b)(2) application relying on the Agency's finding of safety and efficacy for Zofran® I.V. The applicant is proposing the use of an already approved single dose of ondansetron 32 mg I.V. premixed bag which is essentially the same formulation as the Zofran® 32 mg premixed product currently marketed by Glaxo Smith Kline (GSK) except for the use of 0.9% saline diluent rather than a 5% dextrose diluent in the latter product to reflect current clinical preference. The use of either diluent is reflected in the current Zofran vial product. In addition, an alternate new lower single dose ondansetron 8 mg I.V. premixed formulation is also being proposed. The sponsor is seeking only for the indication of prevention of chemotherapy induced nausea and vomiting for both doses. The indication for the prevention postoperative nausea and vomiting (PONV) is not being sought in this submission.

There were no clinical studies performed by the applicant in support of the proposed drug product because they believe that sufficient data are available for the proposed dosing. Their submission is based upon published literature references and the established safety of the Zofran® product.

To support the efficacy of the new lower single dose ondansetron 8 mg injection for the proposed indication, the applicant mainly submitted four studies from published literature written by the following authors: Italian Group for Anti-emetic Research (IGAR), Seynaeve, Ruff, and Beck/Hainsworth. In these studies, ondansetron 8 mg was administered as a single dose prior to chemotherapy, with no follow-up doses for 24 hours; all were designed as randomized, double-blind, active-controlled, multi-center, parallel-group studies. Patients enrolled were naïve to cisplatin and were scheduled to receive cisplatin-containing chemotherapy (≥ 50 mg/m²). The sponsor also submitted seven studies from publications which were regarded as supportive; these studies were not blinded and lacked adequate power to draw statistical conclusions and did not meet the majority of the criteria specified in the FDA Guidance for Industry for Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The applicant also supports this submission with the practice guidelines and recommendations issued by the American Society of Clinical Oncologists (ASCO)¹. In a meeting with the applicant, the Agency communicated to the sponsor that in general, practice guidelines and recommendations are useful but not sufficient to support approval and that the final approvability will be based on the Division's review of the application.

1.3.2 Efficacy

The efficacy data submitted by the sponsor for this NDA has shown that there is a lack of substantial evidence of effectiveness to support the sponsor's proposed new lower single dose ondansetron 8 mg I.V. for the prevention of chemotherapy induced nausea and vomiting (CINV).

Three of the four studies: Seynaeve, Ruff and Beck/ Hainsworth are considered useful for efficacy analysis; the IGAR study is not considered to be useful due to the concomitant use of dexamethasone with ondansetron. The Seynaeve and Ruff studies used an inadequate primary endpoint of *complete plus major response*. The Beck/Hainsworth study was the most useful study to provide efficacy information in which complete protection from emeses (*0 emetic episode*) was evaluated; this study has shown that the single 32-mg dose was superior to the single 8-mg dose in the prevention of CINV.

The Beck and Hainsworth study has shown that a 32 mg single dose (SD) ondansetron I.V. is significantly more efficacious than an 8 mg SD ondansetron I.V. For patients receiving high dose cisplatin, the complete response rate (0 emetic episode) was significantly higher in patients who received a 32 mg SD ondansetron compared to those who received an 8 mg SD ondansetron (48% vs. 35%, $p=0.048$). For patients receiving medium dose cisplatin, the complete response rate (0 emetic episode) was also significantly higher in patients who received a 32 mg SD ondansetron compared to those who received an 8 mg SD ondansetron (73% vs. 50%, $p=0.001$). This study clearly indicates that the 8 mg SD ondansetron did not provide optimal efficacy when compared to the 32 mg SD in the prevention of chemotherapy induced nausea and vomiting.

The Beck and Hainsworth study has also been reviewed as the pivotal trial for the approval of the 32 mg SD ondansetron I.V. under NDA 20-007/S-003 in 1993. The Medical Reviewer concluded that a 32 mg SD ondansetron is significantly more efficacious than an 8 mg SD ondansetron and that the 32 mg SD is more efficacious or at least as efficacious as the standard regimen of 0.15 mg/kg x 3 doses in preventing cisplatin-induced emesis. Although the data failed to show a difference between the ondansetron the single dose 8 mg and the 0.15 mg/kg x 3 doses, the effectiveness of the latter regimen has been established in previously conducted clinical trials and has been approved by the FDA to be an efficacious dose. Moreover, failing to show a difference between the two treatment groups only indicates that there is no sufficient power to reject the null hypothesis of no treatment difference but does not provide evidence to support the equivalence of the two drugs.

¹ Gralla, RJ, Osaba D, et al. Recommendations for the use of antiemetics: Evidence-based, clinical practice guidelines. J Clinical Oncology 1999; 17 (9):2971-94

In addition, the statistical analysis used in the four studies is inadequate and doesn't meet the current standard in which we analyze data in the present research environment and as recommended in the ICH E10 guideline (recommended for adoption on July 20, 2000).

As stated in the ASCO's recommendations, their guidelines cannot be assumed to apply to interventions performed in the context of clinical trials. Clinical studies are designed to test new and novel therapies in which improvement in patient care or treatment is the main goal. This guideline has identified the need for further research and clinical studies investigating the new lower single dose ondansetron 8 mg I.V. Additional clinical data is needed to support the new proposed dose and clinical studies should be conducted using a non-inferiority analysis to an approved dose of ondansetron; the margin of equivalence should be pre-specified in the statistical analysis before conducting the studies.

The information provided in this submission does support the use ondansetron 32 mg single dose in premixed bags as this is an already approved dose for the prevention of chemotherapy induced nausea and vomiting. The proposed product formulation is essentially the same as the 32 mg premixed Zofran product currently marketed by GSK except for the use of saline instead of a dextrose vehicle & the use of flexible plastic container.

1.3.3 Safety

In general, both the 8 mg and 32 mg single dose of ondansetron were well tolerated by patients receiving moderately to highly emetogenic chemotherapy. There were no new safety concerns identified in this submission. The type and incidence of adverse events were similar among the treatment arms in each study.

A detailed review of the safety data from the publications submitted was performed. The safety data in the studies were compared with the safety data of the reference listed drug, Zofran® injection. Since the submission includes published articles and the sponsor had no access to the source data, there were neither narratives nor case report forms (crf) available for review.

In the Seynaeve and Ruff publications, the only adverse events reported were those regarded by the investigator to be related to ondansetron. The IGAR and Beck/Hainsworth publications reported all adverse events regardless of causality.

In the IGAR study, one death was reported, this patient was on granisetron plus dexamethasone; no further information was provided in the publication about this death. In the Seynaeve study, one patient was withdrawn due to an adverse event regarded by the investigator to be unrelated to ondansetron treatment. In addition, two major adverse events were reported: one case of severe constipation and one case of pseudomembranous colitis which resolved spontaneously; no further information was provided regarding these events. No other serious adverse events were reported from the publications.

The most common adverse event consistently reported in patients who received ondansetron in all four studies was headache (9% to 18%); followed by diarrhea, fever and hiccup. In the previous trials with ondansetron, headache was the most common adverse event reported among patients who received ondansetron prior to surgery; while diarrhea (8 to 16%) and headache (17% to 25%) were the most commonly reported in patients receiving chemotherapy. Headache was reported to be generally mild and responded to non-narcotic analgesic. The adverse events reported in this submission were generally consistent with the already known adverse events for ondansetron. Headache, diarrhea, and laboratory changes are the most common likely drug-related adverse events

In the Saynaeve study, no specific laboratory evaluation was pre-specified in the assessment of safety; but it was reported in the results of the study that there were transient changes in the transaminases (ALT/AST) which resolved on follow-up.

As already reported in the prescribing information, elevation of transaminases (AST and ALT) were transient and did not appear to be related to the dose or duration of therapy. These laboratory changes were not associated with any clinical signs and symptoms and resolved spontaneously.

The overall clinical experience for ondansetron is adequate for up to 32 mg single dose injection per day. Ondansetron is an established drug for up to 32 mg single dose injection per day and the dose of 8 mg single dose being proposed is lower than the already approved dose. Because of this, there should not be any specific safety concern with either proposed dose.

1.3.4 Dosing Regimen and Administration

The sponsor is proposing the use of single dose ondansetron 8 mg and 32 mg premixed injection only for the prevention of chemotherapy induced nausea and vomiting. The 32 mg single dose formulation is already approved for this indication. However, the single-dose ondansetron 8 mg injection will be a new lower single dose for the prevention of CINV.

The proposed administration of these premixed formulations will be to infuse over 15 minutes, 30 minutes before the start of emetogenic chemotherapy; this is similar to the administration of the already approved single dose Zofran® 32 mg injection.

This reviewer feels that the proposed administration of 32 mg ondansetron SD I.V. is acceptable. The proposed product formulation is essentially the same as the 32 mg premixed Zofran product currently marketed by GSK except for the use of saline instead of a dextrose vehicle and the use of flexible plastic container. However, the data provided in this submission does not support the approval of the proposed new lower single dose of ondansetron 8 mg I.V.

1.3.5 Drug-Drug Interactions

The concomitant use of apomorphine hydrochloride injection (Apokyn™) with drugs of the 5HT₃ antagonist class (including ondansetron, granisetron, dolasetron, palonosetron, and alosetron) is contraindicated. This is based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron. This is already reflected in the label of Apokyn™.

Ondansetron (Zofran®) is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs. This is reflected in the current label of Zofran.

1.3.6 Special Populations

The sponsor is requesting a waiver for pediatric studies. This request should be granted for the use of single dose ondansetron 32 mg I.V. (an alternate to the multidose regimen of 0.15 mg/kg x 3 doses in adults). This request is acceptable because the use of ondansetron is well-characterized in pediatrics and there is already sufficient information on the use of this product in this population. The current label adequately address pediatric dosing information there are existing age appropriate formulations available for pediatric use. Ondansetron is currently labeled for use in children as young as 6 months old undergoing chemotherapy at a dose of 0.15 mg/kg x 3 doses and in patients as young as 1 month old undergoing surgery at a dose of 0.1 mg/kg single dose. In addition, there are already existing age appropriate formulations available for pediatric use.

However, should the use of a new lower single dose ondansetron 8 mg be approved or pursued by the sponsor in the future, then clinical studies in pediatric patients should be conducted using a new lower single dose ondansetron because this new dose will certainly provide benefit to the pediatric population as an alternate to the multidose regimen of 0.15 mg/kg x 3 doses.

No new information regarding other patient population was submitted in this NDA; therefore, this reviewer refers to the current prescribing information of Zofran.

In adults patients with impaired hepatic function (Child-Pugh score of ≥ 10); a single maximum dose of 8 mg infused over 15 minutes for PONV is recommended. No dosage adjustment is recommended in renally-impaired or geriatric patients.

Ondansetron is excreted in the breast milk of rats but it is not known whether it is excreted in human milk. Caution should be exercised when this drug is administered to a nursing woman because many drugs are excreted in human milk.

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Ondansetron 8 mg and 32 mg IV

Ondansetron is currently listed as Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day and no evidence of impaired fertility or harm to the fetus have been revealed. There are no adequate and well controlled studies in pregnant women; therefore, it should be used during pregnancy only if clearly needed.

**APPEARS THIS WAY
ON ORIGINAL**

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Ondansetron is a selective 5-HT₃ antagonist available as an oral and parenteral antiemetic agent. It preferentially blocks the serotonin 5-HT₃ receptors found centrally in the chemoreceptor trigger zone and peripherally at vagal nerve terminals in the intestines. It is still unknown whether the action of this drug is mediated centrally, peripherally, or a combination of both. Emesis during chemotherapy and radiation therapy appears to be associated with the release of serotonin from enterochromaffin cells in the small intestine. Blocking these nerve endings in the intestines prevents signals to the central nervous system. Ondansetron is also a weak antagonist of the 5-HT₄ receptor, and may bind to other serotonin receptors as well. It has also been demonstrated that it binds to the opioid μ receptor, the clinical implications of which is uncertain. It has no dopamine-receptor blocking activity; multiple oral doses slow colonic transit time.

Ondansetron is indicated for the prevention of chemotherapy induced nausea and vomiting (CINV), postoperative induced nausea and vomiting (PONV) and radiotherapy induced nausea and vomiting (RIV). The intravenous (I.V.) form of ondansetron is only indicated for the prevention of CINV and PONV. The use of ondansetron I.V. formulation for the prevention of chemotherapy induced nausea and vomiting will be the subject of this NDA.

2.2 Currently Available Treatment for Indication

The currently available treatment for the prevention of chemotherapy-induced nausea and vomiting (CINV) are the other currently marketed 5-HT₃ antagonists, namely; dolasetron, granisetron, palonosetron and ondansetron (see table below). Also used for this indication are the dopamine receptor antagonists, metoclopramide (Reglan®), and prochlorperazine (Compazine®); and P/neurokinin 1 (NK-1) receptor-antagonist, aprepitant (Emend®).

Table 1: Currently Approved 5-HT₃s for the Prevention of CINV

Drug	Dose
dolasetron (Anzemet®)	IV: 1.8 mg/kg, 30 minutes before chemotherapy PO: 100 mg, 1 hr. before chemotherapy
granisetron (Kytril®)	IV: 10 mcg/kg, 30 minutes before chemotherapy PO: 2 mg, OD or 1 mg BID
palonosetron (Aloxi®)	IV: 0.25 mg single dose, 30 minutes before chemotherapy
ondansetron (Zofran®)	IV: 32 mg, single dose 30 minutes before chemotherapy or 0.15 mg/kg x 3 doses PO: 24 mg single dose, 30 minutes before chemotherapy

Reviewer's table

2.3 Availability of Proposed Active Ingredient in the United States

Ondansetron is the first selective serotonin blocking agent to be marketed. The injection form was originally approved for the treatment of chemotherapy-induced nausea and vomiting by the FDA on January 4, 1991. Ondansetron is currently available in the form of:

- Injection: 2mg/ml, 32 mg/50 ml premixed
- Tablets: 4 mg, 8 mg, 24 mg
- Orally disintegrating tablets: 4 mg, 8 mg
- Oral solution: 4 mg/5ml

2.4 Important Issues With Pharmacologically Related Products

The concomitant use of drugs in the 5HT₃ antagonist class (including ondansetron, granisetron, dolasetron, palonosetron, and alosetron) with apomorphine hydrochloride injection (Apokyn™) is contraindicated. Apomorphine is a non-ergoline dopamine agonist indicated for the acute, intermittent treatment of hypomobility, "off" episodes associated with advanced Parkinson's disease. This contraindication is based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron. This is already reflected in the label of Apokyn™.

2.5 Presubmission Regulatory Activity

Ondansetron (Zofran®) was developed by GlaxoSmithKline and has been approved for use in the United States for almost 15 years now. It is currently approved for the prevention of chemotherapy, postoperative and radiotherapy induced nausea and vomiting. The recommended intravenous (I.V.) dosing regimen for prevention of chemotherapy-induced (CINV) emesis in adults is a single 32 mg dose administered 30 minutes before the start of emetogenic chemotherapy; or three 0.15 mg/kg doses, the first dose administered 30 minutes prior to chemotherapy with subsequent doses at 4 and 8 hours after the first dose. The sponsor reports that in Europe and Canada, the weight-based dose has been standardized to three 8 mg doses; and alternate dosing regimens, including a single 8 mg dose are also acceptable per the currently approved labeling in those parts of the world.

The sponsor, Baxter Healthcare Corporation, conducted an assessment of common clinical practice in the U.S., and has concluded that there is a market need for an additional premixed presentation of ondansetron hydrochloride injection to facilitate the standard dosing practices commonly observed. The sponsor further reports that clinical practice in the U.S. appears to have a preference for standardized versus weight-based dosing and administration of the lowest therapeutically effective dose. The sponsor also refers to the American Society of Clinical Oncology's (ASCO) recommendations for the administration of serotonin receptor antagonists for the control of emesis induced by chemotherapy; the panel recommended a single dose of 8 mg or 0.15 mg/kg of IV ondansetron.² Because of this, Baxter is proposing to market ready-to-use single-dose infusion bags in two doses: 8 mg and 32 mg only for the treatment of

2 Gralla, RJ, Osaba D, et al. Recommendations for the use of antiemetics: Evidence-based, clinical practice

chemotherapy induced nausea and vomiting. The indication of postoperative nausea and vomiting is not being pursued in this NDA submission.

In addition to an assessment of current dosing practices, the sponsor conducted a literature search for studies that employed a single 8 mg dose of ondansetron in the treatment of nausea and vomiting following chemotherapy to support their submission.

On August 7, 2003, the sponsor and the Agency held a meeting regarding the sponsor's proposed content and format of a 505(b)(2) application for ondansetron hydrochloride injection in intravia container. In this meeting, the sponsor expressed their intention to rely on published reports to support their product approval, the Agency found the approach acceptable; however, it was communicated to the sponsor that the adequacy will depend on the review of the NDA and that each dose and regimen must be adequately supported. The sponsor also inquired if the use of common practice and current standards of care (e.g. Clinical Practice Guidelines and Recommendations from ASCO and approved non-U.S. dosing recommendations) constitute additional and appropriate basis to support the approval of the proposed product and dosing. The Agency responded that in general, practice guidelines and recommendations are useful but not sufficient to support approval and that the final approvability will be based on the Division's review of the application. See meeting minutes dated August 7, 2003 for details.

2.6 Other Relevant Background Information

Ondansetron has been marketed worldwide since 1990 and in the U.S. since 1991, it has not known to be withdrawn from the market due to safety reasons. The safety profile of ondansetron use in both adults and children is well-characterized.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The proposed product formulation is essentially the same as the 32 mg premixed Zofran product currently marketed by GSK except for the varying amounts of ondansetron and the use of saline instead of a dextrose vehicle and the use of flexible plastic container. Each proposed product contain either an 8 mg (0.16 mg/mL) or a 32 mg (0.64 mg/mL) ondansetron as ondansetron hydrochloride (HCl) in 50 mL of 0.9% of sodium chloride and citrate buffered diluent. These premixed injection, USP products are sterile, nonpyrogenic, intravenous solutions for parenteral injection packaged in dual ported 50 mL PL 2408 flexible plastic containers. The table below compares the Zofran marketed products to the sponsor's proposed product. See also Chemistry review for details.

Table 2: Comparison of Zofran Marketed Products to Baxter's Proposed Product

Comparison of ZOFRAN Marketed Products to Baxter's Proposed Product

Ingredient	ZOFRAN Single-Use Glass Vial	ZOFRAN Multi-Use Glass Vial*	ZOFRAN Premixed 50 mL Bag	Baxter's Proposed Premixed 50 mL Bags
Ondansetron	2 mg/mL	2 mg/mL		
Sodium Chloride	9 mg/mL	8.3 mg/mL		
Dextrose	-	-		
Citric Acid Monohydrate	0.5 mg/mL	0.5 mg/mL		
Sodium Citrate Dihydrate	0.25 mg/mL	0.25 mg/mL		
Water for Injection	qs	qs	qs	qs

* Contains parabens as preservatives.

3.2 Animal Pharmacology/Toxicology

No new animal toxicology studies were submitted with this NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data utilized in this review were based on the published studies submitted by the sponsor as listed in the table below as well as other supportive publications. There were no clinical studies conducted by the sponsor to support their submission. The information based on the review of approval of ondansetron 32 mg single-dose (NDA 20-007/S-003) was also used as a source in the review of this NDA.

4.2 Tables of Clinical Studies

**Table 3: Tabular Listing of Publications Submitted by the Sponsor
 (Using 8 mg Single-dose Ondansetron)**

<i>Author & Publication</i>	<i>Objective</i>	<i>Design</i>	<i>Dosage & Administration</i>	<i>Patients</i>	<i>Treatment Duration</i>
IGAR Annals of Oncology 1995; 6:805-10	Compare OND 8 mg IV to GRAN 3mg IV in CIS- induced emesis	Randomized, Double-blind, Active Control, Multicenter, Parallel group, Single-dose	OND: 8 mg IV SD + DXM 20 mg on Day 1; MCP 20 mg PO q6 + DXM 8 mg IM BID on Days 2-4 vs. GRAN: 3 mg IV SD + DXM 20 mg on Day 1; MCP 20 mg PO Q6 + DXM 8 mg IM BID on Days 2-4	483	4 days
				483 (N=966)	
Seynaeve C, et al Br J Cancer 1992; 66: 192-7	Three OND dosing regimens in prophylaxis of CIS-induced emesis	Randomized, Double-blind, Active Control, Multicenter, Parallel group, Single-dose & Multi-dose	8 mg IV prior, then 1 mg/hr for 24 hr vs. 32 mg IV prior, then placebo for 24 hr vs. 8 mg IV prior, then placebo for 24 hr	182	24 hours
				180	
				173 (N=535)	Scheduled to receive CIS (50-120 mg/m ²), naive to CIS therapy 9/89 to 6/90
Ruff P, et al Oncology 1994;51: 113-8	OND (8 and 32 mg) and GRAN (3 mg) in CIS induced emesis	Randomized, Double-blind, Active Control, Multicenter, Parallel group, Single-dose	OND 8 mg IV 20 min prior to CIS vs OND 32 mg IV 20 min prior to CIS vs GRAN 3 mg IV 20 min prior to CIS	165	24 hours
				162	
				169 (N=496)	Scheduled to receive CIS (≥50mg/m ²) naive to CIS therapy 12/91 to 11/92

Beck TM, et al. J Clinical Oncology 1992;10: 1969-75*	Compare OND 8 and 32 mg SD, with OND 0.15 mg/kg x 3 doses	Randomized, Double-blind, Active Control, Multicenter, Parallel group, Single-dose & Multi-dose 26 centers	0.15 mg/kg 30 min prior and 4 and 8 hr vs 8 mg IV SD 30 min prior, then placebo 4 & 8 hrs post vs 32 mg IV SD 30 min prior, then placebo 4 & 8 hr post	234	24 hours
Hainsworth JD, et al.* Seminars in Oncology 1992; 19: 614-19				245	
				220	
				(N=699)	
				Naive pts sched to receive mod (50-70mg/m ²) to high (>100mg/m ²) dose CIS	

* Two publications supporting the same clinical study.

OND-Ondansetron GRAN-Granisetron DXM-Dexamethasone MCP-Metoclopramide

4.3 Review Strategy

Four clinical studies from the published literature were mainly utilized in the review of this NDA. The sponsor also submitted seven studies from publications which were regarded as supportive; these studies were not blinded and lacked adequate power to draw statistical conclusions and did not meet the majority of the criteria specified in the FDA Guidance for Industry for Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. Clinical review for the approval of the single dose Ondansetron 32 mg was also utilized by this Medical Officer. A review of the literature was also conducted to support safety and efficacy.

4.4 Data Quality and Integrity

This NDA is supported by published studies in the literature that were conducted between 1989 and 1994; the sponsor states that attempts were made to obtain or access the original study data but were not successful. Therefore, it was not feasible for Agency to conduct a data audit or inspection. The quality and integrity of the data is unknown based on the submitted publications.

4.5 Compliance with Good Clinical Practices

It is stated in the Hainsworth and Beck publication that all participating institutions received Institutional Review Board approval for the study and each patient gave written informed consent before entering the study. The IGAR study stated that their study was approved by the ethics committees at participating institutions, and all patients gave written or informed consent. The studies by Ruff, et. al and Seynaeve, et.al. both stated that the studies were conducted according to the principles of the Declaration of Helsinki, the study protocol received approval from all local ethics committees and informed consent was obtained from all patients.

4.6 Financial Disclosures

There was no financial disclosure statement submitted by the sponsor. The sponsor submitted publications to support their NDA; therefore, this section is not applicable.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

As reflected in the label, ondansetron is known to undergo extensive metabolism, mainly by hydroxylation, followed by glucuronide or sulfate conjugation. In adults, the mean elimination half-life is 5.7 hours; for those age 15 years and younger, half-life is about 2.4 hours.

In vitro metabolism studies have shown that ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2). Therefore, inducers or inhibitors of these enzymes may change the clearance, hence, the half-life of ondansetron. In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, no dosage adjustment is recommended for patients on these drugs due to limited available data.

In adult patients with mild-to-moderate hepatic impairment, clearance is reduced twofold and mean half-life is increased to 11.6 hours compared to 5.7 hours in normal patients. In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), the maximum total daily dose should not exceed 8 mg (in adults) because clearance is reduced 2 to 3 fold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours.

The concomitant use of apomorphine (a non-ergoline dopamine agonist) with drugs of the 5HT₃ antagonist class (including ondansetron) is contraindicated. This is based on reports of profound hypotension and loss of consciousness when apomorphine hydrochloride was administered with ondansetron. The route of metabolism of apomorphine in humans is not known. The potential routes of metabolism in humans include sulfation, N-demethylation, glucuronidation and oxidation. See Biopharm Review for details.

5.2 Pharmacodynamics

Ondansetron is a selective 5-HT₃ receptor antagonist. It is not certain whether its antiemetic action in chemotherapy-induced emesis is mediated centrally in the chemoreceptor trigger zone of the area postrema or peripherally on the vagal nerve terminals or both.

As reflected in the label, in normal volunteers, single I.V. doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. In another study in six normal male volunteers, a 16-mg dose

infused over 5 minutes showed no effect of the drug on cardiac output, heart rate, stroke volume, blood pressure, or electrocardiogram (ECG). Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. See Biopharm Review for details.

5.3 Exposure-Response Relationships

Not applicable.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

The sponsor is proposing the use of single dose ondansetron 8 mg and 32 mg premixed injection for the prevention of chemotherapy induced nausea and vomiting. The 32 mg single dose formulation is already approved for this indication. However, the lower single-dose ondansetron 8 mg injection will be a new dose for this indication.

These premixed bag formulations will be infused over 15 minutes, 30 minutes before the start of emetogenic chemotherapy. New information regarding the 8 mg single-dose is proposed to be added to the following sections of the label: *Clinical Trials, Indication and Usage, and Dosage and Administration* sections. The sponsor is not pursuing the indication for the prevention of postoperative nausea and vomiting at this time.

The efficacy review was based on the four published studies included in the sponsor's submission. The sponsor also submitted seven studies from publications which were regarded as supportive; these studies were not blinded and lacked adequate power to draw statistical conclusions and did not meet the majority of the criteria specified in the FDA Guidance for Industry for Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. The Clinical Review of NDA 20-007/S-003 by Dr. Hugo Gallo-Torres for the approval of ondansetron 32 mg single-dose was also used by this medical officer as a source in this review.

This Medical Reviewer also worked closely with statisticians, chemists, biopharmaceutical specialists, and a project manager in the review of this submission.

6.1.2 General Discussion of Endpoints

In general, the studies characterized an emetic episode as a single vomit or retch, or any number of continuous vomits or retches that were separated by at least one minute.

Primary Endpoint

The study population included patients who were to receive cisplatin-containing chemotherapy ($\geq 50 \text{ mg/m}^2$), a highly emetogenic chemotherapeutic agent. All the four studies in general assessed protection from emesis; however, each study differed in their primary endpoint. In all of the studies, complete response was defined as no episode of emesis and major response was defined as 1 to 2 episodes of emesis, while the definition of minor and failure varied from each study. See table 4 below.

Table 4: Primary Endpoints

Author	Primary Endpoint		Nausea/Other
IGAR	Complete Protection from emesis (not explicit)	Complete resp=0 Major=1-2 Failure=>3	Nausea (mild, mod, severe)
Seynaeve	Complete + major control of emesis	Complete resp=0 Major=1-2 Minor=3-5 Failure=>5	Nausea (none, mild, mod, severe) Time to 1 st emetic episode
Ruff	Complete + major control of emesis	Complete resp=0 Major=1-2 Failure=>2, resc or w/d	Nausea (mild, mod, severe) Gbl sat VAS 0-100
Beck / Hainswth	No. of emetic episode	Complete resp=0 Major=1-2 Minor=3-5 Failure=>5	Nausea: VAS 0-100 Food intake

Reviewer's table

The most clinically meaningful and acceptable primary endpoint for emesis prevention studies is *complete response* or *no episode of emesis*. This primary endpoint has been successfully utilized in the past for the approval of antiemetic medications. Therefore, the study primary endpoints assessed in the Ruff and Seynave studies are not adequate.

Secondary Endpoint

For the secondary efficacy variable, all of the studies assessed the percentage of patients experiencing mild or no nausea.

In the Beck/Hainsworth study, nausea and food intake were used as secondary efficacy endpoints. Nausea was assessed using a VAS (0=no nausea, 100=nausea as bad as it can be). Food intake was assessed as full meals, light snacks, liquids only, and nothing by mouth.

The IGAR and Seynaeve studies assessed nausea according to a graded scale: 0=none; 1=mild; 2= moderate and 3=severe; in addition, the Seynaeve study also assessed the time to emetic episodes.

In the Ruff trial, nausea (none or mild) and global satisfaction scores (using VAS: 0=not at all satisfied, 100mm=completely satisfied) were assessed.

6.1.3 Study Design

All four studies were designed as randomized, double-blind, active-controlled, multi-center, parallel-group studies. The study population included patients who were naïve to chemotherapy and were receiving cisplatin-containing ($\geq 50 \text{ mg/m}^2$) treatment. In these studies, ondansetron 8 mg was administered as a single dose prior to chemotherapy, with no follow-up doses for 24 hours.

Table 5 below shows some of the characteristics of the study design. A detailed review of the study design of each study are found in the appendix. All of the studies were randomized, double-blind, active-controlled, multicenter, and single or multidose trials. Three studies (Saynaeve, Ruff, & Beck) compared ondansetron 8 mg SD & 32 mg SD.

Table 5: Study Design

Author	Design	Treatment	N
IGAR 12/92 - 7/94	R, DB, AC, MC, Parallel, SD	OND 8 mg + DXM on D1; MCP + DXM on D 2-4 Gran 3 mg + DXM on D1; MCP + DXM on D 2-4	483 483
Seynaeve C, et al 9/89 - 6/90	R, DB, AC, MC, Parallel, SD, MD	OND 8 mg + 1 mg/hr OND 32 mg + PL x 24 hr OND 8 mg + PL x 24 hr	182 180 173
Ruff P, et al 12/91-11/92	R, DB, AC, MC, Parallel, SD	OND 8 mg OND 32 mg Granisetron 3 mg	165 162 169
Beck/ Hw et. al. 1991?	R, DB, AC, MC, Parallel, SD, MD	OND 0.15 mg/kg x 3 doses OND 8 mg then PL 4 & 8 hrs OND 32 mg then PL 4 & 8 hr	234 245 220

One of the major limitations of this submission is in the statistical analysis used in the primary studies. The studies treated the non-significance results for the efficacy comparisons between the different treatment groups as the efficacy equivalence for these different treatment groups; this is not an acceptable statistical analysis. In the current statistical guideline (ICH E10), the margin of equivalence should be pre-specified before conducting the trials. For example, the non-significance result for testing the null hypothesis of no efficacy difference for ondansetron 8 mg versus 32 mg only indicates that no sufficient power to support that the efficacy of the two treatment is different. However, this result does not provide evidence to support the equivalence of the two drugs. See Dr. Wen-Jen Chen's Statistical Review of this NDA for details.

In addition to the above statistical issue, the studies have additional limitations.

Two of the studies, Ruff and Saynaeve used *complete plus major response* as their primary endpoint which is considered by this reviewer as inadequate primary endpoint; complete response or no emetic episode is the most clinically meaningful primary endpoint and which has also been used for the approval of several other 5HT₃'s in the past. The IGAR study used complete response as primary endpoint although not explicit while the Beck/Hainsworth study used number of emetic episode.

The IGAR study, ondansetron was administered in combination with dexamethasone (DXM). The use of DXM can be a potential confounder in this study. While it is true that 5HT₃s are being used by some clinicians in practice in combination with dexamethasone to maximize efficacy, the design of the studies that led to the original approval of ondansetron did not use DXM in combination with ondansetron. Therefore, this medical reviewer does not consider the IGAR study to be useful for the efficacy assessment for ondansetron 8 mg single dose.

The choice of medication for the control group for the other three studies are acceptable.

6.1.4 Efficacy Findings

The four primary studies by IGAR, Seynaeve, Ruff, and Beck/Hainsworth will be reviewed individually for efficacy in this section. In these studies, ondansetron 8 mg was administered as a single dose prior to chemotherapy, with no follow-up doses for 24 hours. As noted above, these four primary publications were submitted by the sponsor to support this NDA which proposes the use of a new lower single dose of ondansetron 8 mg I.V. It is to be noted that the statistical analysis used in all the four these studies as per the current ICH E10 guidance is not adequate. The efficacy findings for each study will nonetheless be presented later in this section.

The Clinical review for the approval of the single dose Zofran 32 mg under NDA 20-007/S-003 (approved in 1993) was also reviewed by this Medical Reviewer since the pivotal study in this NDA (20-007/S-003) included a single-dose ondansetron 8 mg arm. In fact, the Beck/Hainsworth study was the pivotal study submitted by Glaxo-Smith Kline for the approval of single dose Zofran 32 mg I.V. for the prevention of CINV; the Seynaeve study was also reviewed as a supportive trial in the same submission. The Medical Reviewer who reviewed the submission concluded that a single dose 32 mg ondansetron provides superior efficacy compared to the 8 mg single dose.

In the IGAR study, the two treatment groups were reported to be comparable regarding emetic response, nausea control, mean number of emetic episodes, mean time to the first emetic episode, or severity of nausea. Almost 80% of the patients in each treatment group (gran=79.9%; ondan=79.3%) experienced complete protection from emesis and more than 65% of the patients in each treatment group experienced complete protection from both emesis and nausea. The number of patients who reported to receive rescue medications in the first 24 hours was 15 (3%) in the granisetron group and 12 (2.5%) in the ondansetron group.

Table 6: IGAR-Acute Nausea and Vomiting

	Granisetron 3 mg IV SD + dexamethasone N = 483	Ondansetron 8 mg SD IV + dexamethasone N = 483	P-value
Emesis [N (%)] (a)			
Complete Response	386 (79.9%)	383 (79.3%)	0.87
Major Response	52 (10.8%)	51 (10.6%)	NR
Complete + Major Response	438 (90.7%)	434 (89.8%)	NR
Failure	20 (4.1%)	25 (5.2%)	NR
Nausea [N (%)]			
None	347 (71.8%)	348 (72.1%)	1.00
Mild	90 (18.6%)	89 (18.4%)	
Moderate	38 (7.9%)	29 (6.0%)	
Severe	8 (1.7%)	17 (3.5%)	
Nausea and Emesis [N (%)]			
Complete Protection	325 (67.3%)	321 (66.5%)	0.84
Emetic Episodes (b)			
Number of Episodes (Mean ± SD)	3.91 ± 4.3	4.04 ± 4.5	0.83
Mean Time to First Episode (hr)	13.5	13.2	NR
Mean Score of Maximal Intensity of Nausea (c)	1.48 ± 0.6	1.47 ± 0.7	0.90
(a) Emesis response: complete response, 0 episodes; major response, 1-2 episodes; and failure, >3 episodes. (b) Number of patients with vomiting: N = 100 for ondansetron and N = 97 for granisetron. (c) Number of patients with nausea: N = 135 for ondansetron and N = 136 for granisetron. NR = Not reported.			

Sponsor's table

Again, one has to be careful in interpreting the above study results because ondansetron was administered in combination with dexamethasone which is considered to be a confounding factor; hence, this Medical Reviewer does not consider this study to be useful for the efficacy assessment of ondansetron 8 mg SD.

In the Seynaeve study, three doses of ondansetron were compared: patients in Group I received 8 mg followed by 1 mg/hr IV for 24 hours; Group II received 32 mg IV followed by placebo for 24 hours and Group III received 8 mg followed by placebo for 24 hours.

Table 7: Seynaeve, et. al. - Emesis and Nausea Control

	Ondansetron 8 mg IV + 1 mg/hr for 24 hr N=182	Ondansetron 32 mg IV SD N=180	Ondansetron 8 mg IV SD N=173
Emesis Control - Complete + Major	74%	78%	74%
Nausea (None + Mild)			
8 hr	88%	87%	85%
24 hr	77%	73%	75%
Complete emesis control and none or mild nausea	52%	53%	51%
(a) Complete = 0 emetic episodes; Major = 1-2 emetic episodes			

The table above illustrates that complete and major responses was achieved in 74% in the continuous infusion group (I), 78% in the ondansetron 32 mg SD group (II) and 74% in ondansetron 8 mg SD group (III). The pattern of emesis, expressed as the total number of episodes occurring at hourly intervals over 24 hours was similar in the three groups. It also appears that nausea control was comparable among the three groups. No emetic episode and none or mild nausea over 24 hour period was reported by 52% in Group I, 53% in Group II and 51% in Group III. This Medical Reviewer does not consider major response (1-2 emetic episode) as an acceptable primary endpoint.

In the Ruff, et. al. study, it is reported that there were no statistically significant differences between the three treatment groups regarding the number of patients experiencing complete or major emesis control (74% to 78%); or mild or no nausea (69% to 73%). See table below.

Table 8: Ruff, et al: Control of Emesis and Nausea

	Ondansetron 8 mg IV SD N = 165	Ondansetron 32 mg IV SD N = 162	Granisetron 3 mg IV SD N = 169
Emesis Control	N = 164	N = 160	N = 169
Complete (0 emesis)	59%	51%	56%
Major (1-2 emesis)	17%	23%	22%
Complete + Major	76%	74%	78%
Nausea	N = 165	N = 160	N = 169
None	56%	48%	56%
Mild	15%	21%	17%
None + Mild	71%	69%	73%

Sponsor's table

It is to be noted that the primary endpoint prespecified in the publication's statistical analysis was *complete plus major response*. As already previously mentioned, this primary endpoint is

considered not acceptable by this reviewer. In addition, no statistically significant differences between the three treatment groups does not mean that they are of the same efficacy.

The Beck/Hainsworth study, the authors stratified the analyses based on the dose of cisplatin received (high or medium dose).

**Table 9: Beck/Hw-Antiemetic Efficacy in the High-Dose Cisplatin Stratum (> 100 mg/m²)
 Primary Efficacy Variables**

	Ondansetron Dose					
	0.15 mg/kg x 3		8 mg x 1		32 mg x 1	
	No.	%	No.	%	No.	%
No. of patients*	100	100	115	100	102	100
Complete response						
0 EE	41	41	40	35	49	48
Major response						
1 EE	14	14	16	14	14	14
2 EE	5	5	9	8	11	11
Minor response						
3-5 EE	4	4	11	10	8	8
Failure						
> 5 EE or withdrawn/rescued	36	36	39	34	20	20

Abbreviation: EE, emetic episode.
 *Number of patients assessable for antiemetic efficacy.

**Table 10: Beck/Hworth - Antiemetic Efficacy in the Medium-Dose Cisplatin Stratum
 (50 to 70 mg/m²):
 Primary Efficacy Variables**

	Ondansetron Dose					
	0.15 mg/kg x 3		8 mg x 1		32 mg x 1	
	No.	%	No.	%	No.	%
No. of patients*	101	100	107	100	93	100
Complete response						
0 EE	62	61	54	50	68	73
Major response						
1 EE	7	7	12	11	10	11
2 EE	4	4	8	7	4	4
Minor response						
3-5 EE	6	6	8	7	3	3
Failure						
> 5 EE or withdrawn/rescued	22	22	25	23	8	9

*Number of patients assessable for antiemetic efficacy.

The Beck and Hainsworth study has shown that a 32 mg single dose (SD) ondansetron I.V. is significantly more efficacious than an 8 mg SD ondansetron I.V. For patients receiving high dose cisplatin, the complete response rate (0 emetic episode) was significantly higher in patients who received a 32 mg SD ondansetron compared to those who received an 8 mg SD ondansetron (48% vs. 35%, p=0.048). For patients receiving medium dose cisplatin, the complete response

rate (0 emetic episode) was also significantly higher in patients who received a 32 mg SD ondansetron compared to those who received an 8 mg SD ondansetron (73% vs. 50%, $p=0.001$). This study clearly indicates that the 32 mg SD ondansetron provides optimal efficacy when compared to the 8 mg SD in the prevention of chemotherapy induced nausea and vomiting.

It is also reported in the publication that there were no statistically significant differences between the standard three-dose regimen and the single 8-mg ondansetron dose. Although it is reported in the publication that there were no statistically significant differences between the standard three-dose regimen and the single 8-mg ondansetron dose, one should be very careful in interpreting this statement because having no statistical difference between these two groups does not mean that they are of the same efficacy. This could simply mean that there is not enough information to show that they are different. Moreover, although the data failed to show a difference between the single dose 8 mg and the 0.15 mg/kg x 3 dosing regimen, the effectiveness of the latter regimen has been established in previous trials & has been previously approved by the FDA.

The Beck/Hainsworth study has been reviewed as the pivotal trial for the approval of the Zofran® 32 single dose I.V. under NDA 20-007/S-003. The following are the medical reviewer's conclusion regarding the study:

- for the prevention of chemotherapy induced nausea and vomiting, a single dose 32 mg ondansetron provides superior efficacy vs. single dose 8 mg
- a single dose 32 mg provides equivalent, if not superior efficacy vs. 0.15 mg/kg x 3 doses
- the data failed to show a difference between the ondansetron 0.15 mg/kg x 3 vs. the single dose ondansetron 8 mg.

6.1.5 Clinical Microbiology

A microbiology consult was requested for these premixed formulation in plastic containers and their review is pending at this time.

6.1.6 Efficacy Conclusions

The efficacy data from the publications submitted by the sponsor is not sufficient to support the sponsor's proposed new lower single dose ondansetron 8 mg I.V. in premixed bags for the prevention of chemotherapy induced nausea and vomiting.

Only three studies: Seynaeve, Ruff and Beck/ Hainsworth are considered useful for efficacy analysis; the IGAR is not considered to be a useful study due to the concomitant use of dexamethasone with ondansetron. The Seynaeve and Ruff studies used an inadequate primary endpoint of complete plus major response. The Beck/Hainsworth study was the most useful study to provide efficacy information; this study has shown evidence that the single 32-mg dose was superior to the single 8-mg dose in the prevention of CINV.

The Beck and Hainsworth study has shown that a 32 mg single dose ondansetron I.V. is significantly more efficacious than a 8 mg single dose (SD) ondansetron I.V. For patients receiving high dose cisplatin, the complete response rate (0 emetic episode) was significantly higher in patients who received a 32 mg SD ondansetron compared to those who received an 8 mg SD ondansetron (48% vs. 35%, $p=0.048$). For patients receiving medium dose cisplatin, the complete response rate (0 emetic episode) was also significantly higher in patients who received a 32 mg SD ondansetron compared to those who received an 8 mg SD ondansetron (73% vs. 50%, $p=0.001$). This study clearly indicates that the 32 mg SD ondansetron provides optimal efficacy when compared to the 8 mg SD in the prevention of chemotherapy induced nausea and vomiting.

The Beck and Hainsworth study has also been reviewed as the pivotal trial for the approval of the 32 SD ondansetron I.V. under NDA 20-007/S-003 in 1993. The Medical Reviewer concluded that a 32 mg SD ondansetron is significantly more efficacious than an 8 mg SD ondansetron; the 32 mg SD is more efficacious or at least as efficacious as the standard regimen of 0.15 mg/kg x 3 doses in preventing cisplatin-induced emesis. Although the data failed to show a difference between the ondansetron single dose 8 mg and the 0.15 mg/kg x 3 doses, the effectiveness of the latter regimen has been established in previously conducted clinical trials and has been approved by the FDA to be an efficacious dose. Moreover, failing to show a difference between the two treatment groups only indicates that there is no sufficient data to reject the null hypothesis of no treatment difference but does not provide evidence to support the equivalence of the two drugs.

In addition, the statistical analysis used in these studies is inadequate and doesn't meet the current standard in which we analyze data in the present research environment and as recommended in the ICH E10 guideline (adopted July 20, 2000).

As stated in the ASCO's recommendations, their guidelines cannot be assumed to apply to interventions performed in the context of clinical trials. Clinical studies are designed to test new and novel therapies in which improvement in patient care or treatment is the main goal. This guideline has identified the need for further research and clinical studies investigating the new lower single dose ondansetron 8 mg I.V. Additional clinical data is needed to support the new proposed dose and clinical studies should be conducted using a non-inferiority analysis to an approved dose of ondansetron; the margin of equivalence should be pre-specified in the statistical analysis before conducting the studies.

The information provided in this submission supports the use of ondansetron 32 mg single dose in premixed bags, an already approved dose for the prevention of chemotherapy induced nausea and vomiting. The proposed product formulation is essentially the same as Zofran 32 mg premixed product currently marketed by GSK except for the use of saline instead of a dextrose vehicle and the use of flexible plastic container.

7 INTEGRATED REVIEW OF SAFETY

7.1 *Methods and Findings*

A detailed review of the safety data from the publications submitted was performed. The safety data in the studies were compared with the safety data of the reference listed drug, Zofran® injection. Since the submission includes published articles and the sponsor had no access to the source data, there were neither narratives nor case report forms (crf) available for review.

7.1.1 Deaths

One death was reported in the IGAR study, this patient was on granisetron plus dexamethasone. There was no further information provided in the publication about this death. There was no source data or crf available for review.

7.1.2 Other Serious Adverse Events

There were no other serious adverse events reported from the publications.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

One patient in the IGAR study who was on granisetron and dexamethasone was reported to be lost to follow up. One patient in the Seynaeve study who was on ondansetron treatment was reported to be withdrawn due to an adverse event; the adverse event was reported to be unrelated to ondansetron. In both instances, the specific details on the patient were not provided.

7.1.3.2 Adverse events associated with dropouts

There was only one patient (Seynaeve study) who was reported to be withdrawn due to an adverse event, but this was considered by the investigator to be unrelated to ondansetron treatment. There is no crf or source data available for this reviewer to evaluate this event.

7.1.3.3 Other significant adverse events

In the Synaeve study, two major adverse events reported: one case of severe constipation and one case of pseudomembranous colitis. These resolved spontaneously. No further information was provided regarding these events.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the IGAR study it is stated that adverse events were assessed by general questioning at each evaluation during the first 24 hours; thereafter, patients were required to report any adverse events on their log cards from day 2 to 6. The other three studies did not provide information on how adverse events were elicited. In the Seynaeve and Ruff publications, the only adverse events that were reported were those regarded by the investigator to be related to ondansetron. The IGAR and Beck/Hainsworth publications reported all adverse events regardless of causality. In any study, adverse events should be reported regardless of relationship to the study drug.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

It was not reported in the publications what the investigators used to report adverse events. It is reported that the severity of adverse events and the relationship to the study treatment was assessed by the investigator.

7.1.5.3 Incidence of common adverse events

The most common adverse event consistently reported in patients who received ondansetron in all four studies was headache (9% to 18%); followed by diarrhea, fever and hiccup. In the previous trials with ondansetron, headache was the most common adverse event reported among patients who received ondansetron prior to surgery; while diarrhea (8 to 16%) and headache (17% to 25%) were the most commonly reported in chemotherapy patients. Headache was reported to be generally mild and responded to non-narcotic analgesic. The adverse events reported in this submission were generally consistent with the already known adverse events for ondansetron. Below is tabulated incidence of headache in the four primary studies.

Table 11: Incidence of Headache in the Four Studies

Publication	Ondansetron 8 mg IV SD	Ondansetron 32 mg IV SD	Ondansetron 8 mg IV SD + 1mg/hr	Ondansetron 0.15 mg/kg x 3	Granisetron 3 mg IV single dose
IGAR	-	-	3%*	-	3%*
Seynaeve	12%	14%	9%	-	-
Ruff	12%	10%	-	-	7%
Beck/Hw	18%	25%	-	18%	-

Reviewer's table

* plus dexamethasone

7.1.5.4 Common adverse event tables

The most common adverse events are tabulated below. It is to be noted that in the Seynaeve and Ruff studies, only adverse events that were regarded as the investigator to have causality with the antiemetic treatment were reported. See table below for combined adverse event data from the four primary studies.

Table 12: Combined Adverse Event Data from the Four Primary Studies

	Ondansetron 8 mg IV SD N=1066	Granisetron 3 mg IV SD N=652	Ondansetron 32 mg IV SD N=562	Ondansetron 8 mg IV SD + 1 mg/hr N=182	Ondansetron 0.15 mg/kg x 3 N=234
Headache	99 (9%)	26 (4%)	96 (17%)	16 (9%)	43 (18%)
Other	31 (3%)	20 (3%)	14 (2%)	11 (6%)	0 (0%)
Diarrhea	23 (2%)	0 (0%)	28 (5%)	3 (2%)	25 (11%)
Fever	19 (2%)	0 (0%)	16 (3%)	0 (0%)	26 (11%)
Hiccup	16 (2%)	11 (2%)	0 (0%)	0 (0%)	0 (0%)
ALT/AST Incr.	2 (<1%)	0 (0%)	7 (1%)	4 (2%)	0 (0%)
ALT Increased	5 (1%)	0 (0%)	7 (1%)	0 (0%)	5 (2%)
AST Increased	7 (1%)	0 (0%)	7 (1%)	0 (0%)	9 (4%)
Flushing	10 (1%)	14 (2%)	2 (<1%)	2 (1%)	0 (0%)
Weakness	4 (<1%)	11 (2%)	0 (0%)	0 (0%)	0 (0%)
Epigastric Pain	4 (<1%)	5 (1%)	0 (0%)	0 (0%)	0 (0%)
Nervousness	4 (<1%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Constipation	3 (<1%)	7 (1%)	3 (1%)	3 (2%)	0 (0%)
Sedation	2 (<1%)	5 (1%)	0 (0%)	0 (0%)	0 (0%)
Heartburn	1 (<1%)	4 (1%)	0 (0%)	0 (0%)	0 (0%)
Dizziness	1 (<1%)	1 (<1%)	3 (1%)	0 (0%)	0 (0%)
Xerostomia	0 (0%)	0 (0%)	3 (1%)	1 (1%)	0 (0%)

Sponsor's table

7.1.5.5 Identifying common and drug-related adverse events

Headache, diarrhea, and laboratory changes are the most common likely drug-related adverse events.

7.1.6 Less Common Adverse Events

There were no report of less common adverse events identified which raises any safety concern.

7.1.7 Laboratory Findings

No information regarding laboratory evaluation was provided in the IGAR and Ruff study.

There was limited data regarding laboratory evaluations provided. The Beck/Hainsworth study monitored CBC and biochemistry at baseline and at the end of 24 hour study period; abnormal values considered to be related to ondansetron were followed-up until they return to normal or otherwise explained. It was reported that there was no significant differences observed between the treatment groups with respect to laboratory indices of safety.

In the Saynaeve study, no specific laboratory evaluation was pre-specified in the assessment of safety; but it was reported in the results that there were transient changes in the transaminases (ALT/AST) which resolved on follow-up.

As already reported in the prescribing information, elevation of transaminases (AST and ALT) were transient and does not appear to be related to the dose or duration of therapy. These laboratory changes were not associated with any clinical signs and symptoms and resolved spontaneously.

7.1.8 Vital Signs

Since the studies were from published articles, there was no protocol available to indicate how patients were assessed with regards to vital signs. The publications did not provide any information as to as to how vital signs were monitored.

7.1.9 Electrocardiograms (ECGs)

No information regarding ECGs monitoring was provided in the publications. The prescribing information for Zofran IV states under the cardiovascular adverse events section that rare cases of angina (chest pain), ECG alterations, hypotension and tachycardia have been reported and that in many cases, the relationship to Zofran is unclear.

7.1.10 Immunogenicity

No information regarding immunogenicity was provided in the publications.

7.1.11 Human Carcinogenicity

This NDA did not include human carcinogenicity studies. The carcinogenic potential of ondansetron was assessed by the sponsor on the reference listed drug, Zofran I.V. The following information is included in the prescribing information for Zofran I.V.

The current package insert for ondansetron states that carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg per day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity and

oral administration up to 15 mg/kg per day did not affect fertility or general reproductive performance of male and female rats.

7.1.12 Special Safety Studies

No special safety studies were included in this submission.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Ondansetron has no known potential for drug abuse or dependence.

7.1.14 Human Reproduction and Pregnancy Data

There is no new information human reproduction or pregnancy data included in this submission. It is already known that ondansetron is a pregnancy category B. Reproduction studies have been performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

7.1.15 Assessment of Effect on Growth

The sponsor did not assess the effect of ondansetron on growth.

7.1.16 Overdose Experience

There is no specific antidote for ondansetron overdose and patients should be managed with appropriate supportive therapy. Individual doses as large as 150 mg and total daily dosages (three doses) as large as 252 mg have been administered intravenously without significant adverse events. These doses are more than 10 times the recommended daily dose.

In addition to the known adverse events of ondansetron, the following events have been described in the setting of ondansetron overdose: "sudden blindness" (amaurosis) of 2 to 3 minutes' duration plus severe constipation occurred in one patient that was administered 72 mg of ondansetron intravenously as a single dose, hypotension (and faintness) occurred in another patient that took 48 mg of oral ondansetron. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the events resolved completely. This information is already included in the package insert of Zofran®.

7.1.17 Postmarketing Experience

Ondansetron has been marketed worldwide since 1990 and in the U.S. since 1991, it has not known to be withdrawn from the market due to safety reasons. The safety profile of ondansetron use in both adults and children is well-characterized.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The primary source of clinical data for the safety review was from the publications submitted by the sponsor and the Agency's finding of safety for ondansetron. A total of 2,698 patients were included in the four pivotal studies; of which 1,066 patients received at least single dose of ondansetron 8 mg, 652 patients received a single dose of granisetron 3 mg, and 562 patients received a single dose of ondansetron 32 mg. All studies were randomized, double blind, double-blind, active control, multicenter, parallel group, single or multidose studies. Three of the studies (IGAR, Seynaeve and Ruff) were conducted in Europe while one study (Beck/Hainsworth) was conducted in the U.S.

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7.2.1.2 Demographics

Table 13: Demographic Summary for Primary Studies

	Ondansetron 8 mg IV SD N=1066	Granisetron 3 mg IV SD N=652	Ondansetron 32 mg IV SD N=562	Ondansetron 8 mg IV SD + 1 mg/hr N=182	Ondansetron 0.15 mg/kg x3 N=234
Gender (N, %)					
Male	679 (64%)	415 (64%)	331 (59%)	82 (45%)	157 (67%)
Female	387 (36%)	237 (36%)	231 (41%)	100 (55%)	77 (33%)
Age (yr)					
Mean	55 (1 study)	55 (1 study)	54 (1 study)	n/a	n/a
Median	61 (3 studies)	61 (1 study)	61 (2 studies)	57.5 (1 study)	61 (1 study)
Cisplatin Dose (N, %)					
<50 mg/m ²	35 (3%)	329 (50%)	27 (5%)	11 (6%)	0 (0%)
≥50 mg/m ²	1031 (97%)	323 (50%)	535 (95%)	171 (94%)	234 (100%)
Primary Tumor Site (N, %)					
Lung	383 (36%)	234 (36%)	185 (33%)	30 (16%)	107 (46%)
Gyne- cological	199 (19%)	122 (19%)	127 (23%)	67 (37%)	14 (6%)
Head/Neck	161 (15%)	96 (15%)	110 (20%)	31 (17%)	41 (18%)
Genito- urinary	131 (12%)	77 (12%)	58 (10%)	28 (15%)	20 (9%)
Other	128 (12%)	104 (16%)	34 (6%)	11 (6%)	21 (9%)
GI	55 (5%)	15 (2%)	34 (6%)	15 (8%)	23 (10%)
Bone/soft tissue	11 (1%)	2 (<1%)	11 (2%)	3 (2%)	8 (3%)

Sponsor's table

There were more males than females in the four primary studies (59% vs. 49%). The age range of patients was 19 to 82 years old and the median age was 51 years of age. Majority of the patients received cisplatin at a dose of ≥ 50 mg/m². It is to be noted that there were four primary studies submitted and the demographics of each study is discussed in detail in the appendix section of this review. The five treatment arms as tabulated below were not necessarily compared with each other; therefore, balance among the treatment groups (per column) should not be expected.

7.2.1.3 Extent of exposure (dose/duration)

The dose and duration of ondansetron administered to patients in the study are equal to or lesser than the already approved dose and duration of ondansetron. Therefore, the exposure to ondansetron in the primary studies is acceptable. However, the dose of the comparator drug granisetron in the IGAR and Ruff studies is higher than the approved U.S. dose, although approved in Europe, where the studies were conducted.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The safety data from the reference listed drug, Zofran I.V. were compared to the data in the primary studies submitted. There were no other clinical data sources utilized in this safety review.

7.2.2.1 Other studies

Not applicable

7.2.2.2 Postmarketing experience

Ondansetron has been marketed worldwide since February 23, 1990 and in the United States since January 4, 1991. In the United States alone, more than — prescriptions have been written since approval. There has been substantial experience with its successful use in the prevention of nausea and vomiting associated with highly emetogenic chemotherapy, as well as in the management of postoperative nausea and vomiting.

The safety profile of ondansetron use in both adults and children is well-characterized. It has never been withdrawn from any market for any safety reason.

7.2.2.3 Literature

A search of the current literature did not identify any specific safety concern for ondansetron.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience for ondansetron is adequate for up to 32 mg I.V. single dose per day. Ondansetron is an established drug for up to 32 mg I.V. single dose per day and the dose of 8 mg I.V. single dose being proposed is lower than the already approved dose. Because of this, there should not be any specific safety concern with any of the proposed doses.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There were no new animal studies submitted with this NDA.

7.2.5 Adequacy of Routine Clinical Testing

There were no information provided regarding routine clinical testing submitted with this NDA.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This submission did not provide any information regarding metabolic, clearance and interaction workup.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor did not conduct any pharmacokinetic or drug interaction studies.

7.2.8 Assessment of Quality and Completeness of Data

This NDA includes only published literature, there were no source data provided. Therefore, the quality of the data cannot be assessed.

7.2.9 Additional Submissions, Including Safety Update

No additional submissions were provided.

7.3 *Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions*

The most common adverse event consistently reported in patients who received ondansetron in all four studies was headache (9% to 18%); followed by diarrhea, fever and hiccup. In the previous trials with ondansetron, headache was the most common adverse event reported among patients who received ondansetron prior to surgery; while diarrhea (8 to 16%) and headache (17% to 25%) were the most commonly reported in chemotherapy patients. Headache was reported to be generally mild and responded to non-narcotic analgesic. The adverse events reported in this submission were generally consistent with the already known adverse events for ondansetron.

7.4 *General Methodology*

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable.

7.4.2 Explorations for Predictive Factors

Not applicable

7.4.3 Causality Determination

Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor is proposing the use of single dose ondansetron 8 mg and 32 mg premixed injection only for the prevention of chemotherapy induced nausea and vomiting. The 32 mg single dose formulation is already approved for this indication. However, the single-dose ondansetron 8 mg injection will be a new lower dose for the prevention of CINV.

The proposed administration of these premixed formulations will be to infuse over 15 minutes, 30 minutes before the start of emetogenic chemotherapy; this is similar to the administration of the already approved Zofran® 32 mg injection.

This reviewer feels that the proposed administration of ondansetron 32 mg single dose I.V. is acceptable. The proposed product formulation is essentially the same as the 32 mg premixed Zofran product currently marketed by GSK except for the use of saline instead of a dextrose vehicle & the use of flexible plastic container. However, the data provided in this submission does not support the approval of the proposed new lower single dose of ondansetron 8 mg I.V.

8.2 Drug-Drug Interactions

The concomitant use of apomorphine with drugs of the 5HT₃ antagonist class (including ondansetron, granisetron, dolasetron, palonosetron, and alosetron) is contraindicated. This is based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.

Ondansetron (Zofran®) is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs. This is reflected in the current label of Zofran.

8.3 Special Populations

No new information regarding other patient population was submitted in this NDA; therefore, this reviewer refers to the current prescribing information of Zofran.

In adults patients with impaired hepatic function (Child-Pugh score \geq of 10), a single maximum dose of 8 mg infused over 15 minutes for PONV is recommended. No dosage adjustment is recommended in renally-impaired or geriatric patients.

Ondansetron is excreted in the breast milk of rats but it is not known whether it is excreted in human milk. Caution should be exercised when this drug is administered to a nursing woman because many drugs are excreted in human milk.

Ondansetron is currently listed as Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day and no evidence of impaired fertility or harm to the fetus have been revealed. There are no adequate and well controlled studies in pregnant women; therefore, it should be used during pregnancy only if clearly needed.

8.4 Pediatrics

The sponsor is requesting a waiver for pediatric studies; this request should be granted for the use of single dose ondansetron 32 mg I.V. (an alternate to the multidose regimen of 0.15 mg/kg x 3 doses in adults). This request is acceptable as the use of ondansetron is well-characterized in pediatrics and there is already sufficient information on the use of this drug in this population. It is currently labeled for use in children as young as 6 months old undergoing chemotherapy at a dose of 0.15 mg/kg x 3 doses and in patients as young as 1 month old undergoing surgery at a dose of 0.1 mg/kg single dose. In addition, there are already existing age appropriate formulations available for pediatric use.

However, should the use of a new lower single dose ondansetron 8 mg be approved or pursued by the sponsor in the future, then clinical studies in pediatric patients should be conducted using a new lower single dose ondansetron because this new lower single dose will certainly provide benefit to the pediatric population as an alternate to the multidose regimen of 0.15 mg/kg x 3 doses.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

Current literature review did not identify any specific safety concerns.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan for this NDA.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

This NDA supports the approval of single dose ondansetron 32 mg injection but not the proposed new lower single dose ondansetron 8 mg injection for the prevention of chemotherapy induced nausea and vomiting. The proposed ondansetron 32 mg injection formulation is essentially the same as the already approved premixed Zofran® 32 mg injection currently marketed by GSK except for the use of saline instead of a dextrose vehicle and the use of flexible plastic container. However, there is lack of substantial evidence to support the approval of the proposed single dose ondansetron 8 mg injection. The data presented has shown that the 32 mg SD ondansetron I.V. provide a significantly superior efficacy than the 8 mg SD ondansetron I.V. in the prevention of chemotherapy induced nausea and vomiting.

The applicant mainly submitted four studies from published literature written by the following authors: Italian Group for Anti-emetic Research (IGAR), Seynaeve, Ruff, and Beck/Hainsworth to support the efficacy of a new lower SD ondansetron 8 mg for the prevention of CINV. These studies were identified by the sponsor in which ondansetron 8 mg was administered as a single dose prior to chemotherapy, with no follow-up doses for 24 hours. All were designed as randomized, double-blind, active-controlled, multi-center, parallel-group studies. Patients enrolled were naïve to cisplatin and were mostly receiving cisplatin-containing chemotherapy (≥ 50 mg/m²). Unlike the three studies in which ondansetron was administered as the sole antiemetic, the IGAR study evaluated the combination of ondansetron and dexamethasone to control emesis. The latter study is considered not useful in supporting the proposed indication.

The primary endpoint defined in the Ruff and Seynaeve studies was complete plus major response (≤ 2 emetic episodes) while in the Beck/Hainsworth study, the primary endpoint was number of emetic episode. The basis of approval of other antiemetics such as 5HT₃s has been complete response or no emetic episode because this is the most clinically meaningful endpoint. Therefore, this NDA leaves us with the Beck/Hainsworth study as the pivotal study in evaluating the proposed new lower single dose ondansetron 8 mg. This study has been utilized by GSK and has been the pivotal trial reviewed by the Agency in the past which led to the approval of a single dose ondansetron 32 mg injection as an alternate to the multidose regimen.

The sponsor of this NDA, Baxter, claims efficacy equivalence/similarity of ondansetron 8 mg to the approved doses of ondansetron (32 mg single dose or 0.15 mg x 3 doses) based upon the non-significant result shown in the superiority analysis reported by the three selected trials (Ruff, Beck/Hainsworth, and Seynaeve). However, in statistics, non-significance only indicates that no sufficient information to reject the null hypothesis of no treatment difference but does not provide evidence to support the equivalence of the two drugs. Therefore, clinical trials are needed to evaluate the effectiveness of a new lower single dose ondansetron 8 mg I.V. compared to an approved dose of Zofran for the prevention of chemotherapy induced nausea and vomiting.

9.2 Recommendation on Regulatory Action

This medical reviewer recommends the approval of the already approved proposed single dose ondansetron 32 mg I.V. presented in a 0.9% saline diluent in 50 mL IntraVia flexible plastic containers for the prevention of chemotherapy induced nausea and vomiting.

However, this Medical Reviewer *does not* recommend the approval of the proposed new lower single dose ondansetron 8 mg I.V. for the prevention of chemotherapy induced nausea and vomiting.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are required at this time.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

See Appendix A for this Medical Reviewer's recommendations for labeling changes

9.5 Comments to Applicant

The sponsor should consider conducting Phase 3 clinical studies in cancer patients to evaluate the effectiveness of a new lower single dose ondansetron 8 mg I.V. compared to an approved dose

Clinical Review
Lolita A. Lopez, M.D.
NDA 21-915
Ondansetron 8 mg and 32 mg IV

of Zofran for the prevention of chemotherapy induced nausea and vomiting applying the principle recommended by ICH Guideline E10.

The sponsor should modify the label according to the above labeling recommendations.

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10 APPENDICES

10.1 Labeling Recommendation

Below are my recommendations for labeling changes to the sponsor's proposed label. In general, information pertaining to the new lower single dose ondansetron 8 mg should be deleted from the proposed label.

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Clinical Review
Lolita A. Lopez, M.D.
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Medical Officer Comments: The above deleted information dose to is not applicable to the 32 mg single dose premixed formulation.

10.2 Review of Individual Study Reports

The four publications by the following authors: Italian Group for Anti-emetic Research (IGAR), Seynaeve, Ruff, and Beck/Hainsworth will be reviewed individually in this section. In these studies, ondansetron 8 mg was administered as a single dose prior to chemotherapy, with no follow-up doses for 24 hours. All four studies were designed as randomized, double-blind, active-controlled, multi-center, parallel-group studies. Patients were naïve to chemotherapy and were receiving cisplatin-containing ($\geq 50 \text{ mg/m}^2$) treatment.

Italian Group for Anti-emetic Research (IGAR) Study Ann Oncol 1995;6:805-10

Ondansetron versus Granisetron, both Combined with Dexamethasone, in the Prevention of Cisplatin-Induced Emesis

Study Dates: December 1992 to July 1994

The study was conducted at more than five centers in Italy.

Medical Officer Comments: It is not clear what the exact number of centers were in this study, "more than five centers" could be anywhere from 6 to 20 centers.

Study Design

This was a randomized, double-blind, active-controlled, multi-center, parallel-group, single-dose study. A total of 973 patients adult patients scheduled to receive cisplatin-containing therapy ($\geq 50 \text{ mg/m}^2$) either alone or combined with other chemotherapeutic agents were included in the study. Single doses of ondansetron 8 mg IV or granisetron 3 mg IV were administered following dexamethasone (DXM) 20 mg on Day 1 approximately 15 minutes prior to chemotherapy. On Days 2-4, 20 mg of oral metoclopramide was administered every six hours, and intramuscular DXM was administered as 8 mg twice daily on Days 2-3 and 4 mg twice daily on Days 4-5.

Study Population:

The exclusion criteria were:

- nausea or vomiting or use of anti-emetics in the 24 hours before cisplatin chemotherapy
- severe concurrent illness other than neoplasia
- other causes of vomiting (e.g., GI obstruction, CNS metastases, hypercalcemia)
- contraindications to dexamethasone (active PUD, GI bleeding due to peptic ulcer)
- concurrent therapy with corticosteroids (unless given as physiological supplements)
- benzodiazepines (unless given for night sedation)
- abdominal radiotherapy or pregnancy.

Medical Officer Comments: It is not specified which antiemetics were excluded for use in the study. The source data is not available to verify what concomitant medications patients are taking. It was not stated if females who are lactating and of child bearing potential were excluded. If included, it was not stated if and what method of contraception was used.

Treatment:

All patients received dexamethasone (DXM) 20 mg in 50 ml saline given as IV infusion over 15 minutes, 45 minutes prior to cisplatin administration. Patients were then administered the following:

Day 1: Ondansetron 8 mg IV single dose or granisetron 3 mg IV (both meds in 50 ml. saline) infusion over 15 mins., 15 minutes prior to chemotherapy.

After the infusion of ondansetron or granisetron, cisplatin was infused over 30 minutes.

Days 2-4: Metoclopramide 20 mg po q 6 hours and DXM IM 8 mg on days 2 to 3, and 4 mg twice daily on days 4 to 5.

Medical Officer Comments: The approved dose of granisetron in the United States is 10 µg/kg weight or around 1 mg for an average weight person. The study was also conducted using the 5HT₃ medication in combination with DXM. The use of DXM can be a potential confounder in this study. While it is true that 5HT₃s are being used by some clinicians in practice in combination with dexamethasone to maximize efficacy, the design of the studies that led to the approval of ondansetron did not use dexamethasone in combination with ondansetron.

The U.S. approved label of granisetron states that the IV infusion time for the diluted preparation is 5 minutes.

Response Assessment

Nausea, emesis and adverse effects were recorded every 2 hours for the first 8 hours after cisplatin and then daily for 6 days.

An emetic episode was defined as a single vomit or retch, or any number of continuous vomits or retches that were separated by an absence of vomiting or retching for at least one minute. Emesis control during the first 24 hours was scored as follows:

- complete response = 0 episode
- major response = 1-2 episodes
- failure = >3 episodes.

Nausea was graded on a four-point scale:

- none
- mild = did not interfere with daily life

- moderate = interfered with daily life
- severe = bedridden because of nausea.

If a patient failed to respond (3 or more emetic episode) in the first 24 hours, he or she could receive rescue medication such as:

- diphenhydramine 50 mg IV + DXM 8 mg + metoclopramide 4 mg/kg for inpatients or
- DXM 8 mg IM for outpatients

Statistical Methodology

The primary endpoint for this study was *complete control* of acute emesis (i.e., within 24 hours posttreatment). Analyses of nausea and vomiting were done separately for Day 1 (acute emesis) and Days 2-6 (delayed emesis). The chi-squared test with Yate's correction and Fisher's Exact test, when there was a low frequency in at least one cell, were used to evaluate the balance of prognostic factors between the two experimental groups, as well as to compare the difference in efficacy of the two anti-emetic treatments and the frequency of side effects.

The number of patients included in the trial was calculated on the assumption that complete control of acute emesis would be achieved in 75% of patients treated with ondansetron plus DXM, and at a rate not greater or smaller than 10% with respect to ondansetron plus DXM with the combination of granisetron plus DXM.

A total of 920 patients were required to detect a significant difference with 90% probability if granisetron plus DXM were at least 10% less efficacious than ondansetron plus DXM. If granisetron plus DXM were at least 10% more efficacious than ondansetron plus DXM the power of the study was 90%.

Logistic linear models were performed to evaluate the treatment effect adjusted for each of the other prognostic factors, as well as the second order interactions between treatment and each of the other prognostic factors to detect subgroups of patients, if any, in whom the two treatments had a different efficacy. A multifactorial analysis, using logistic linear models was performed. Comparisons were made between experimental groups [*mean time to the first emetic episode, mean number of emetic episodes* (considering only the patients who vomited), and mean maximum intensity of nausea (if applicable)] using the Mann-Whitney U test. All p values refer to two-tailed tests.

Results

Patient Accounting

A total of 973 patients were recruited for the study, of which 966 were evaluated for efficacy according to the intention-to-treat principle (ITT). Three patients in the ondansetron plus DXM were excluded from the efficacy analysis due to:

- 1 - error in the administered antiemetic treatment and case report form not completed
- 1 - refusal of chemotherapy
- 1 - chemotherapy was different from cisplatin after randomization

Four patients receiving granisetron plus DXM were excluded from the efficacy analysis due to:

- 1 death during the first 24 hours
- 2 failed to receive antiemetic therapy after randomization
- 1 lost to follow-up

Medical Officer Comments: The cause and details of the death of one patient in the ondansetron plus DXM group was not provided and cannot be obtained due unavailability of the source data. It is also not clear to me why one patient was lost to follow up since patients were in the hospital during the first 24 hours of the study when the assessment for acute vomiting was done. Also, the publication states that no information was provided regarding the number of subjects withdrawn from the study.

Patient Demographics

Patient characteristics for the evaluable patients are presented in the table below. Overall, there were more males than females who participated in the study (68% vs. 32%). There were more males in the ondansetron group than the granisetron group; opposite is true for the females. The two treatment groups were otherwise well-matched for age, alcohol use, tumor site, cisplatin dose, and concomitant chemotherapy. The most common malignancy (38-39%) was lung cancer.

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Table A1: IGAR Study Demographics

	Granisetron 3 mg IV SD + dexamethasone N = 483	Ondansetron 8 mg IV SD + dexamethasone N = 483
Gender (N, %)		
Male	317 (65.6%)	340 (70.4%)
Female	166 (34.4%)	143 (29.6%)
Median Age (yr)	61	61
Alcohol Use (N, %)		
≤7 U/week	233 (48.2%)	235 (48.7%)
>1 U/day	250 (51.8%)	248 (51.3%)
Cisplatin Dose		
<90 mg/m ²	307 (63.6%)	302 (62.5%)
≥90 mg/m ²	176 (36.4%)	181 (37.5%)
Concomitant Chemotherapy (N, %)		
Anthracyclines ± Others	126 (26.0%)	142 (29.4%)
Low Emetogenicity	250 (51.8%)	234 (48.4%)
5-Fluorouracil	54 (11.2%)	54 (11.2%)
Cyclophosphamide ± Others	53 (11.0%)	53 (11.0%)
Primary Tumor Site (N, %)		
Ovary	70 (14.5%)	71 (14.7%)
Lung	189 (39.1%)	182 (37.7%)
Head-Neck	57 (11.8%)	55 (11.4%)
Bladder	63 (13.1%)	75 (15.5%)
Other	104 (21.5%)	100 (20.7%)

Sponsor's table module 5 p.10

Efficacy

The table below shows the assessment of nausea, vomiting, or both. The two treatment groups were comparable regarding emetic response, nausea control, mean number of emetic episodes, mean time to the first emetic episode, or severity of nausea. More than 65% of the patients in each treatment group experienced complete protection from emesis and nausea. The number of patients who received rescue medications in the first 24 hours was 15 (2.8 %) in the granisetron group and 12 (2%) in the ondansetron group.

Table A2: Acute Nausea and Vomiting (IGAR)

	Granisetron 3 mg IV SD + dexamethasone N=483	Ondansetron 8 mg SD IV + dexamethasone N=483	P-value
Emesis [N (%)] (a)			
Complete Response	386 (79.9%)	383 (79.3%)	0.87
Major Response	52 (10.8%)	51 (10.6%)	NR
Complete + Major Response	438 (90.7%)	434 (89.8%)	NR
Failure	20 (4.1%)	25 (5.2%)	NR
Nausea [N (%)]			
None	347 (71.8%)	348 (72.1%)	1.00
Mild	90 (18.6%)	89 (18.4%)	
Moderate	38 (7.9%)	29 (6.0%)	
Severe	8 (1.7%)	17 (3.5%)	
Nausea and Emesis [N (%)]			
Complete Protection	325 (67.3%)	321 (66.5%)	0.84
Emetic Episodes (b)			
Number of Episodes (Mean ± SD)	3.91 ± 4.3	4.04 ± 4.5	0.83
Mean Time to First Episode (hr)	13.5	13.2	NR
Mean Score of Maximal Intensity of Nausea (c)	1.48 ± 0.6	1.47 ± 0.7	0.90
(a) Emesis response: complete response, 0 episodes; major response, 1-2 episodes; and failure, >3 episodes. (b) Number of patients with vomiting: N=100 for ondansetron and N=97 for granisetron. (c) Number of patients with nausea: N=135 for ondansetron and N=136 for granisetron. NR= Not reported			

Sponsor's table module 5 p.11

Medical Officer Comments: In the table presented, acute nausea and vomiting efficacy results, it is not clear whether the results were obtained after 8 hours or 24 hours of cisplatin administration. It is assumed that the results above are from a 24 hour assessment period, although not clear from the publication. Although the number of patients who received rescue medications is reported, there is no information as to how many times rescue medications were administered for each patient. Although efficacy was also evaluated for protection from delayed (>24 hours) nausea and vomiting, such information will not be reviewed in this submission.

At the multifactorial analysis, the effect of prognostic factors (gender, age, cisplatin dose, kinetosis, type of neoplasia, alcohol intake, concomitant chemotherapy, treatment setting, concomitant non-chemotherapeutic medications, and naïve/pretreated status) on the efficacy of the two study medications was examined. The analyses indicate that with granisetron administration, patients with kinetosis were significantly less protected from emesis. Ondansetron seems to be slightly more efficacious than granisetron in patients who had previously received chemotherapy.

Medical Officer Comments: The number of patients with kinetosis in this study is too small (granisetron group=12%; ondansetron 8.3%) too make a generalized valid conclusion regarding the kinetosis and the study treatment. The same is true with chemotherapy naïve patients where there was only 6.6 % in the granisetron group and 7.3 % in the ondansetron group. The number of patients is too small to make a generalized conclusion.

The publication states that 956 patients were evaluable for clinical efficacy, causes of non-evaluation were: dose of cisplatin <45 mg/m² (4), concurrent use of benzodiazepins (2) or corticosteroids (1), cerebral metastases (2) and previous cisplatin chemotherapy (1). No source data or crf are available to check the details of these patients. Moreover, in the acute nausea and vomiting (table 2 of the publication), a total of 966 patients were included in the efficacy of evaluation. It is not clear whether these 10 non-evaluable patients were included in the efficacy evaluation.

Safety

One death was reported in the IGAR study, this patient was on granisetron plus dexamethasone. There was no further information provided in the publication about this death. There was no source data or crf available for review.

The most frequently reported adverse events in either group during the first 24 hours were: headache, hot flushes, hiccups, and weakness.

Table A3: Adverse Events Reported During the First 24 Hours (IGAR)

Edverse Event	Granisetron 3 mg IV SD + dexamethasone N = 484	Ondansetron 8 mg SD IV + dexamethasone N = 483	P-value
Constipation	3	2	0.99
Headache	15	15	0.86
Heartburn	4	1	0.37
Weakness	11	4	0.12
Epigastric Pain	5	4	0.99
Nervousness	1	4	0.37
Hot-Flush	14	10	0.54
Hiccup	11	16	0.43
Sedation	5	2	0.45
Other	20	21	0.99

Medical Officer Comments: It is to be noted that the dose of granisetron used in this study is three times the approved U.S. dose, therefore, the adverse events are expected to be higher; on the other hand, the ondansetron dose used is only one third of the approved dose. In the approved label of granisetron, at 10 mcg/kg dose, the five most common

adverse events are: headache, asthenia, somnolence, diarrhea and constipation. In addition, it will be difficult to attribute the above AEs to ondansetron or granisetron alone due to the co-administration of dexamethasone.

Seynaeve C, et al. Study

Br J Cancer 1992; 66:192-7

Comparison of the Anti-Emetic Efficacy of Different Doses of Ondansetron, Given as Either a Continuous Infusion or a Single Intravenous Dose, in Acute Cisplatin-Induced Emesis. A Multicentre, Double-Blind, Randomised, Parallel Group Study

Study Dates

September 1989 to June 1990.

Study Centers

More than 25 investigators in 11 countries: Austria, Belgium, Germany, Finland, Holland, Denmark, Iceland, Israel, Luxembourg, Spain and the United Kingdom.

Ethics

The study protocol was approved by local Hospital Ethics Committees and the study was conducted according to the principles of the Declaration of Helsinki.

Study Design

This was a randomized, double-blind, active-controlled, multi-center, parallel-group, multi-dose study. A total of 535 patients who were scheduled to receive their first course of cisplatin (50-120 mg/m²) either alone or in combination of other cytotoxic drugs were enrolled:

- 182 patients received ondansetron 8 mg IV 30 minutes prior to chemotherapy, followed by 1 mg/hr IV for 24 hours
- 180 patients received ondansetron 32 mg IV 30 minutes prior to chemotherapy, followed by placebo for 24 hours
- 173 patients received ondansetron 8 mg IV 30 minutes prior to chemotherapy, followed by placebo for 24 hours.

Study Population

Patients who were scheduled to receive their first course of cisplatin (50-120 mg/m²) either alone or in combination of other cytotoxic drugs were included.

The exclusion criteria were:

- episode of nausea or vomiting and/or received anti-emetic therapy in the 24-hour period prior to the start of treatment
- serious concurrent illness other than cancer or another etiology for emesis
- concurrent use of corticosteroids (except for physiological supplementation)

- concurrent use of benzodiazepines (unless given for night sedation).

Medical Officer Comments: In this study, as in the IGAR study, the antiemetic therapy prohibited was not specified and there was no statement regarding the disposition of females who are lactating, pregnant or of child bearing potential. The source data is not available regarding concomitant medication use.

Treatment

The loading dose of either:

- 8 mg ondansetron loading dose plus 1 mg/hr x 24 hours (group I)
- 32 mg ondansetron loading dose plus same volume of saline x 24 hours (group II)
- 8 mg ondansetron loading dose plus same volume of saline x 24 hours (group III)

Ondansetron was diluted in 100 ml of saline, and administered over 15 min starting 30 min prior to the initiation of the cisplatin infusion. The cisplatin infusion was set up 15 min after the start of the continuous infusion and run over 1 – 4 h.

Medical Officer Comments:

It should be noted that one of the comparator treatment (8 mg ondansetron loading dose plus 1 mg/hr x 24 hours) is not an approved regimen.

The design states that the loading dose was diluted in 100 ml of saline, however, it was not clear what how much saline or fluid was used for the continuous infusion. The sponsor currently proposes dilution of ondansetron 50 ml of saline, however, this study was not conducted as it is proposed in the label.

Assessment of efficacy and side effects

All patients were monitored in the hospital for the 24 h after the start in the cisplatin infusion. A single emetic episode was defined as a single vomit or retch (vomit not productive of liquid), or any number of continuous vomits or retches, each episodes was separated by the absence of symptoms for at least 1 min.

The overall response criteria for emesis were:

- complete response (CR) = 0 emetic episodes
- major response (MR) = 1 – 2 emetic episodes
- minor response (MR) = 3 - 5 emetic episodes
- failure (F) = >5 emetic episodes.

The timing and number of emetic episodes were recorded and cross-checked with the patient. Patients who experienced three or more emetic episodes and were rescued with additional anti-emetic medication were considered to be treatment failures.

Nausea was assessed by the patient before treatment, and at 8 and 24 h after treatment, using a four-point graded scale:

- none
- mild – did not interfere with normal daily life
- moderate – interfered with daily life
- severe – bedridden due to nausea

Medical Officer Comments: Failure in this Seynaeve study is defined as >5 emetic episodes; there was no mention of any rescue medications given.

Statistical Methodology

The primary endpoint for this study was *complete and major control of acute emesis* (within 24 hours post-treatment).

The required number of patients was calculated under the assumption that complete and major anti-emetic control would be achieved in 75% of the patients with the continuous infusion schedule (8 mg+1 mg/hr). Using two-sided tests at an overall 5% significance level and a power of 0.8, 170 (of which 150 could be expected to be evaluable) would be required in each group to detect a difference of at least 15% between the continuous infusion regimen and the either of the single dose regimens (8 mg and 32 mg).

All analyses were performed on the intent-to-treat analysis population (ITT) providing efficacy data were available. The proportions of patients showing a complete or a complete plus major response were compared between treatments using a two-sided Mantel-Haenszel chi-squared test stratified by center. The *time to first emetic episode* was compared for all pairs of treatment using Wilcoxon rank sum analysis. A separate analysis was also carried out after stratification by country, using the Van Elteren method for combining Wilcoxon statistics over strata. The grades of nausea for the 8 and 24 hr after chemotherapy were analyzed using the stratified, extended Mantel-Haenszel method. Subset analysis for the difference in gender, cisplatin dose and concurrent chemotherapy was carried out using the chi-squared test of 2x2, 2x3 and 2x4 tables.

Medical Officer Comments: The primary endpoint used is the complete and major control of acute emesis (1–2 emetic episodes) within 24 hours post-treatment. This not an acceptable primary endpoint. The most clinically meaningful endpoint is complete response or no emetic episode.

Results

Patient Accounting

A total of 535 patients were enrolled in the study and randomized: 182 in the 8 mg + 1 mg/hr; 180 in the 32 mg dose and 173 in the 8 mg + placebo. There were 42 patients who did not comply with the protocol:

- 18 received an incorrect cisplatin dose schedule
- 12 received concurrent anti-emetics
- 7 were not naïve to chemotherapy
- 4 had severe concurrent illnesses
- 1 was withdrawn due to an adverse event that was unrelated to ondansetron.

The publication states that the analyses of the efficacy results of the total and the evaluable populations did not reveal any differences in the overall conclusions.

Medical Officer Comments: Details regarding early withdrawal from the study due to an adverse event were not provided and cannot be verified due to the unavailability of source data.

Patient Demographics

The three treatment groups were well balanced for age, gender, alcohol intake, primary tumor site, cisplatin dose, duration of cisplatin infusion, and concomitant chemotherapy. Females comprised 51% of the population and males comprised 49% and the median age was 59 years. The most common tumors were gynecological in nature (37%) followed by lung cancer (21%).

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**Table A4: Demographics
 (Seynaeve)**

	Ondansetron			Total N=535
	8 mg + 1 mg/hr N=182	32 mg IV SD N=180	8 mg IV SD N=173	
Gender (N, %)				
Male	82 (45%)	95 (53%)	86 (50%)	263 (49%)
Female	100 (55%)	85 (47%)	87 (50%)	272 (51%)
Median Age (yr)	57.5	60	60	59
<7 Alcohol Units Intake/wk	143 (79%)	140 (78%)	132 (76%)	415 (78%)
Concurrent Chemotherapy				
None	58	57	63	178
Cyclophosphamide	32	37	36	105
Epi doxorubicin	17	14	11	42
CY epi doxorubicin	13	8	11	32
Eto teniposide	18	21	19	58
5-Fluorouracil	16	17	14	47
Miscellaneous	28	26	19	73
Cisplatin Dose				
<50 mg/m ²	11 (6%)	6 (3%)	10 (6%)	27 (5%)
50- <70 mg/m ²	79 (43%)	66 (37%)	70 (40%)	215 (40%)
70- <100 mg/m ²	58 (32%)	62 (34%)	66 (38%)	186 (35%)
≥100 mg/m ²	34 (19%)	46 (26%)	27 (16%)	107 (20%)
Primary Tumor Site				
Head and Neck	31 (17%)	30 (17%)	27 (16%)	88 (16%)
Lung	30 (16%)	41 (23%)	39 (23%)	110 (21%)
Gastrointestinal	15 (8%)	10 (6%)	9 (5%)	34 (6%)
Genitourinary	28 (15%)	22 (12%)	25 (15%)	75 (14%)
Gynecological	67 (38%)	66 (37%)	65 (38%)	200 (37%)
Bone Soft Tissue	3 (2%)	3 (2%)	4 (2%)	10 (2%)
Miscellaneous	11 (6%)	13 (7%)	11 (6%)	35 (7%)

Data extracted from publication. Typographical errors have not been corrected.
 Sponsor's table, module 5 p.15

Medical Officer Comments: It should be noted that in this study that the proportion of patients who received cisplatin ≥ 100mg/m² was 20% (107/535): 27/173 (16%) in the 8 mg single dose ondansetron group; 34/182 (19%) in the 8 mg single dose ondansetron plus continuous infusion; and 46/180 (26%) in the 32 mg single dose ondansetron group. There were a total of 27/535 (5%) patients who received <50mg/m² of cisplatin; the study should have only included patients on cisplatin at a dose of 50-120mg/m². In the patient accounting, it is stated that 18 patients were not evaluable because they received an incorrect cisplatin dose schedule. No further details was provided.

Efficacy

Results for the control of acute emesis are shown in the figure below.

Figure 1: Control of Acute Emesis

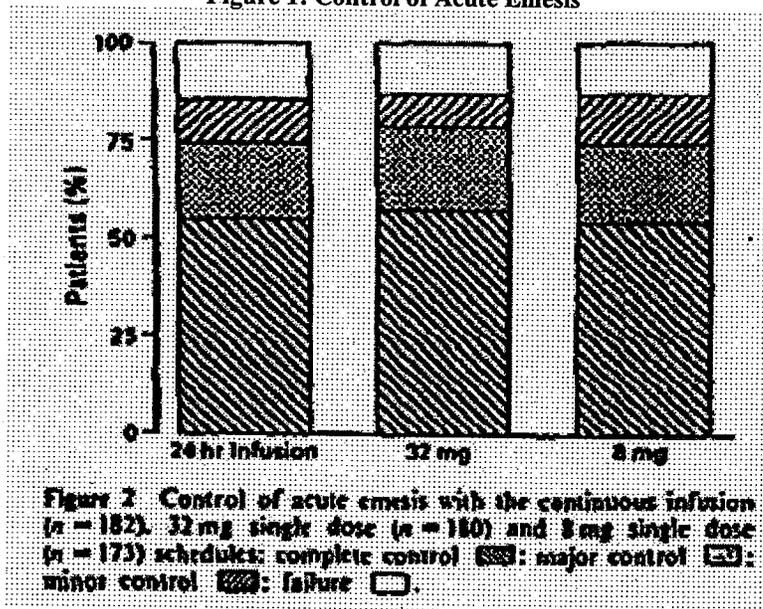


Table from the publication, Seynaeve et al.

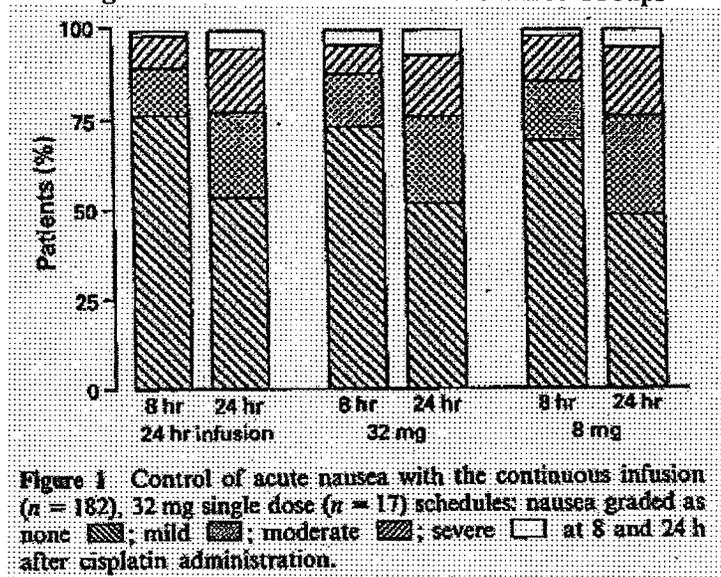
The figure above illustrates that complete and major responses was 74% in Group I, 78% in Group II and 74% in Group III. The pattern of emesis, expressed as the total number of episodes occurring at hourly intervals over 24 hours was similar in the three groups. The percentage of patients with none or mild nausea after 24 hours were 77% in group I, 75% in groups II and III. From this figure, it appears that there is similarity in emetic control achieved with the three groups for complete and major response combined.

No emetic episode and none or mild nausea over 24 hour period was reported by 52% in Group I, 53% in Group II and 51% in Group III.

Medical Officer Comments:

The publication states that no emetic episode and none or mild nausea over 24 hour period was reported by 52% in Group I, 53% in Group II and 51% in Group III. However, it is not clear how these percentages were obtained; there is no available data to verify this information.

Figure 2: Control of Nausea in the Three Groups



Above figure taken from publication, Seynaeve, et. al.

Medical Officer Comments: It is to be noted that most clinically meaningful response is complete control of emesis and no nausea. Major response (1-2 emeses) is not an acceptable primary endpoint to primarily support the indication and the proposed new lower single dose of ondansetron 8 mg.

Prognostic factors:

It is reported in this publication that proportions of patients with complete responses stratified on the basis of gender, cisplatin dose and concomitant chemotherapy showed that complete control of emesis was achieved in a higher proportion of male patients (67% vs. 43%, P<0.001) and in patients receiving lower cisplatin doses [65% (<70 mg/m²) vs. 48% (≥70 mg/m²)], P<0.001.

Medical Officer Comments: Even though there were more males than females that appears to have a higher percentage of complete responses, it was not stated in the publication if it took into consideration other underlying factors that contributed to the outcome such as tumor site, dose of chemotherapy, concurrent therapy, age, past history of motion sickness, etc.; the same is true for the of dose of cisplatin administered.

Safety

The only adverse events that are regarded by the investigator to be related to ondansetron were reported in this publication. The most commonly reported events considered by the investigator to be possibly, probably or almost certainly related to ondansetron were headache (11%). It is reported that none of these patients were withdrawn from the study; the symptoms resolved spontaneously or were treated with mild analgesics. The next

most common adverse events were diarrhea and changes in laboratory values (both 3% of all patients). (See table below).

Severe constipation and pseudomembranous colitis, and elevations in ALT and AST were identified as being possibly related to ondansetron . Both the constipation and colitis resolved spontaneously. All changes in ALT and AST resolved at follow-up, and none were associated with any clinical signs or symptoms.

There was one patient who was withdrawn due to an unrelated adverse event, but details were not provided in the publication.

Table A5: Adverse Events (Seynaeve, et.al)

	Ondansetron			Total N = 535
	8 mg + 1 mg/hr N = 182	32 mg IV SD N = 180	8 mg IV SD N = 173	
Headache	16 (9%)	25 (14%)	20 (12%)	61 (11%)
Diarrhea	3 (2%)	5 (3%)	5 (3%)	13 (3%)
Laboratory Changes	4 (2%)	7 (4%)	2 (1%)	13 (3%)
Constipation	3 (2%)	3 (2%)	0 (0%)	6 (1%)
Flushing	2 (1%)	2 (1%)	0 (0%)	4 (1%)
Xerostomia	1 (1%)	3 (2%)	0 (0%)	4 (1%)
Miscellaneous	11 (6%)	14 (8%)	10 (6%)	35 (7%)

Adverse events considered by the investigator to be possibly, probably or almost certainly related to ondansetron.

Medical Officer Comments: Only adverse events that are regarded by the investigator to be related to ondansetron were reported in this publication. All adverse events experienced by the patients in a clinical trial should be reported regardless of causality. The severity of adverse events should also be reported; serious adverse events should be reported separately.

There were 13/535 (3%) patients who were reported to have elevated ALT and AST. It appears from the table above that there were more patients in the 32 mg single dose ondansetron group who had the most number of patients with enzyme elevation; however, these could have been mild elevations. It is important to know the degree of elevation of these liver enzymes but there no source data available to look into the details and the actual values.

Table A6 : Adverse Events (Seynaeve, et al)

	Ondansetron			Total N=535
	8 mg + 1 mg/hr N=182	32 mg IV SD N=180	8 mg IV SD N=173	
Headache	16 (9%)	25 (14%)	20 (12%)	61 (11%)
Diarrhea	3 (2%)	5 (3%)	5 (3%)	13 (3%)
Laboratory Changes	4 (2%)	7 (4%)	2 (1%)	13 (3%)
Constipation	3 (2%)	3 (2%)	0 (0%)	6 (1%)
Flushing	2 (1%)	2 (1%)	0 (0%)	4 (1%)
Xerostomia	1 (1%)	3 (2%)	0 (0%)	4 (1%)
Miscellaneous	11 (6%)	14 (8%)	10 (6%)	35 (7%)

Sponsor's submission module 5 p.17

Medical Officer Comments: This study has been reviewed by the Agency in 1993 as a supportive trial for the approval of Ondansetron 32 mg single dose I.V. for the prevention of chemotherapy induced nausea and vomiting under NDA 20-007/S-003. The Medical Reviewer, Dr. Hugo Gallo-Torres stated in the review that both the continuous infusion regimen (32 mg total) and the 32 mg single dose regimen were numerically superior to the 8 mg single dose regimen.

Ruff P, et al.
 Oncology 1994;51:113-8

Ondansetron Compared with Granisetron in the Prophylaxis of Cisplatin-Induced Acute Emesis: A Multicentre, Double-Blind, Randomised, Parallel Group Study

Study Dates: December 1991 to November 1992.

Study Centers: A total of 42 centers in 7 countries: Denmark, France, Germany, the Netherlands, South Africa, Switzerland and the United Kingdom.

Ethics: The study was conducted according to Good Clinical Practice and to the Declaration of Helsinki (1964) as modified by the 41st World Medical Assembly, Hongkong, 1989. The protocol received approval from all regulatory authorities and local ethics committees as appropriate to the countries in which the study was carried out. Written consent was obtained from patients after an explanation of the study had been given.

Study Design

This was a randomized, double-blind, active-controlled, multi-center, parallel-group, single-dose study. A total of 496 patients were enrolled; they were scheduled to receive their first course of cisplatin ($\geq 50 \text{ mg/m}^2$)-containing chemotherapy. Patients were randomly assigned to receive a single dose of one of three IV anti-emetic regimens: ondansetron 8 mg, ondansetron 32 mg, or granisetron 3 mg.

Study Population

Patients, aged at least 18 years, who were scheduled to receive their first dose of cisplatin chemotherapy at a dose of $\geq 50 \text{ mg/m}^2$ administered as a single intravenous infusion given over a period of up to four hours either alone or in combination with other cytotoxics were enrolled.

Exclusion Criteria:

- received non-cisplatin chemotherapy during the previous 6 months
- had a severe concurrent illness (other than cancer)
- had other etiologies for emesis (e.g., GI obstruction, CNS metastases)
- had received anti-emetic therapy 24 hours prior to chemotherapy
- had received benzodiazepines (except for night sedation)
- concurrent corticosteroids (except for physiological supplementation, bone metastases or respiratory problems)
- had vomited within 24 hours prior to chemotherapy
- pregnant

Medical Officer Comments: It was not specified how much corticosteroid is allowed, patients could be on a high dose systemic steroids for other problems. The use of high dose steroids could be a potential confounding factor. It was not specified if females who are lactating were excluded and if females of child-bearing potential used an effective means of contraception in this study.

Treatment

Patients were randomly assigned to receive a single dose of one of three IV anti-emetic regimens:

- ondansetron 8 mg
- ondansetron 32 mg
- granisetron 3 mg

Each loading dose was diluted to 50 mL in normal saline and administered over 15 minutes starting 20 minutes prior to the cisplatin infusion.

Medical Officer Comments: The approved dose of granisetron is 10 mcg/kg or usually around 1 mg per dose in an average weight person. The dose of graniseeron (3 mg) used in this study as a comparator drug is not approved dose in the U.S; therefore, this should not be an acceptable comparator drug.

Assessment

An emetic episode was defined as a single vomit or retch. Emetic episodes were, by definition, separated by the absence of both vomiting and retching for at least 1 minute. Emesis control during the first 24 hours after cisplatin infusion was scored as follows:

- complete response = 0 episodes
- major response = 1-2 episodes
- failure = >2 episodes, rescued or withdrawn due to lack of response

Nausea, which was graded on a four-point scale (none, mild, moderate and severe), was assessed separately at 24 hours following chemotherapy. Global satisfaction with the anti-emetic treatment was recorded by the patient at 24 hours after the start of cisplatin using a 100 mm VAS.

Statistical Methodology

The primary analysis was performed on all patients who were randomized and received the study treatment and cisplatin chemotherapy (intent-to-treat population, ITT). The primary endpoint for the study was *complete or major* control of acute emesis (within 24 hours post-treatment). Sample size was determined based on the assumption that complete or major control of emesis would be achieved in 75% of patients in the ondansetron 32 mg group. Using two-sided tests at an overall 5% significance level and a power of 0.8, approximately 450 patients (150 patients in each treatment group) would be required to detect a difference of at least 15% between ondansetron 32 mg and either of the other two treatment groups (ondansetron 8 mg and granisetron 3 mg).

The safety analysis was performed on all patients who were randomized and who received study treatment. All analyses of efficacy data were stratified by cluster of centers. Clusters were based on country and, where appropriate, geographical region within the country and ranged in size between 33 and 73 patients. The proportions of patients showing (1) complete emetic response, (2) complete or major emetic response or (3) no emesis and no nausea were compared between treatments using stratified Mantel-Haenszel chi-squared tests. Nausea grades and global satisfaction scores were compared between treatments using stratified Wilcoxon rank sum tests. The effects of potential prognostic factors (e.g., age, gender) on complete or major emetic response and their interaction with treatment were assessed using logistic regression models. Fisher's exact tests were used to analyze the proportions of patients experiencing adverse events.

Results

Patient Accounting

A total of 497 patients were included in the final safety analysis; one patient did not receive cisplatin and therefore was excluded from the ITT analysis. A total of 496 patients were included in the ITT analysis.

- 165 patients were randomized to the 8 mg ondansetron group
- 162 patients were randomized to the 32 mg ondansetron group
- 169 patients were randomized to the 3 mg granisetron group

Data concerning screening failures or early withdrawals were not presented.

Patient Demographics

The three treatment groups appears to be well balanced for age, gender, body surface area, alcohol use, tumor site, cisplatin dose, and concomitant chemotherapy. The median cisplatin dose was 78 mg/m² and the most common malignancy in all three treatment groups was gynecological tumors (30%). See table below.

Table A7: Demographics

	Ondansetron		Granisetron	Total N = 496
	8 mg IV SD N = 165	32 mg IV SD N = 162	3 mg IV SD N = 169	
Gender (N, %)				
Male	93 (56%)	88 (54%)	98 (58%)	279 (56%)
Female	72 (44%)	74 (46%)	71 (42%)	217 (44%)
Mean Age (yr)	55	54	55	55
Alcohol Use (N, %)				
Current >4 units/day	16 (10%)	14 (9%)	15 (9%)	45 (9%)
Previous >4 units/day	25 (15%)	28 (17%)	23 (14%)	76 (15%)
Cisplatin Dose				
< 50 mg/m ²	25 (15%)	21 (13%)	22 (13%)	68 (14%)
50- <70 mg/m ²	45 (27%)	56 (35%)	54 (32%)	155 (31%)
70- <100 mg/m ²	72 (44%)	65 (40%)	65 (38%)	202 (41%)
≥100 mg/m ²	23 (14%)	20 (12%)	28 (17%)	71 (14%)
Emetogenic Potential of Concurrent Chemotherapy				
None	41 (25%)	44 (27%)	39 (23%)	124 (25%)
Low	71 (43%)	66 (41%)	72 (43%)	209 (42%)
Moderate	53 (32%)	51 (31%)	57 (34%)	161 (32%)
High	0 (0%)	1 (1%)	1 (1%)	2 (0%)
Most Common Tumor Site (a)				
Gynecological	49 (30%)	49 (30%)	52 (31%)	150 (30%)
Lung	45 (27%)	36 (22%)	45 (27%)	126 (25%)
Head and Neck	34 (21%)	39 (24%)	39 (23%)	112 (23%)
Genito-urinary	15 (9%)	15 (9%)	14 (8%)	44 (9%)
Gastrointestinal	12 (7%)	11 (7%)	15 (9%)	38 (8%)
Bone/Soft Tissue	5 (3%)	4 (2%)	2 (1%)	11 (2%)

(a) N = 165 for ondansetron 8 mg, 163 for ondansetron 32 mg, 169 for granisetron, and 497 for total. Since only most common tumor sites are presented, numbers may not sum to total.

Sponsor's table

Medical Officer Comments: It is to be noted that there were 68 patients (14%) who received cisplatin at a dose of <math><50\text{ mg/m}^2</math> [ondansetron 8 mg group=25/165 (15%) or 5% of the total study population; ondansetron 32 mg group=21/162 (13%) or 4% of the total population; granisetron 3 mg group=22/165 (13%) or 4% of the total population]. One wonders if these patients should have been regarded as protocol deviations. There is no source data to verify the actual dose received by patients since <math><50\text{ mg/m}^2</math> is a broad dose. These patients could have an effect on efficacy. It will be interesting to know how these patients responded to the emetic control evaluation.

Efficacy

The reported anti-emetic response in this study is shown in the table below. It is reported in the study that there were no statistically significant differences between the three treatment groups regarding the number of patients experiencing complete or major emesis control (range of 74% to 78%), or mild or no nausea (range of 69% to 73%). The following is also reported for no emesis and no nausea over the 24 hour period: ondansetron 8 mg=47%; ondansetron 32 mg =36%; and granisetron 3mg =45%.

Table A8: Control of Emesis and Nausea (Ruff, et al)

	Ondansetron 8 mg IV SD N = 165	Ondansetron 32 mg IV SD N = 162	Granisetron 3 mg IV SD N = 169
Emesis Control	N = 164	N = 160	N = 169
Complete (0 emesis)	59%	51%	56%
Major (1-2 emesis)	17%	23%	22%
Complete + Major	76%	74%	78%
Nausea	N = 165	N = 160	N = 169
None	56%	48%	56%
Mild	15%	21%	17%
None + Mild	71%	69%	73%

Medical Officer Comments: The primary endpoint of complete or major control of acute emesis (within 24 hours post-treatment) is not acceptable. The most clinically meaningful endpoint should be complete response or no emesis within 24 hours post treatment.

It appears from the table above that patients in the ondansetron 8 mg single dose group and the granisetron 3 mg group had a numerically higher percentage of complete emesis and no nausea control compared to the 32 mg ondansetron group. It is reported in the publication that there were no statistically significant differences with respect to complete or major response between the three anti-emetic treatment. It was not specified what p values were used and there are no available source data to verify these results.

There appears to be no evidence of interaction between treatments and prognostic factors (age, gender, alcohol use, cisplatin dose or concomitant chemotherapy) on complete or major response in this study.

Adverse Events

The only adverse events reported in this publication were the ones considered investigator to be possibly, probably or almost certainly related to the study anti-emetic treatments were reported in this publication.

The most commonly reported drug-related adverse events for all treatment groups was headache (15%), followed by diarrhea, constipation and dizziness (see table below). No severe or unexpected drug-related adverse events were observed with ondansetron or granisetron. No severe or unexpected adverse events were reported. No further safety information was presented.

Table A9: Incidence of Drug-Related Adverse Events (Ruff, et al)

	Ondansetron 8 mg IV SD N = 165	Ondansetron 32 mg IV SD N = 163	Granisetron 3 mg IV SD N = 169
Any Event	24 (15%)	25 (15%)	15 (9%)
Headache	20 (12%)	16 (10%)	11 (7%)
Diarrhea	2 (1%)	5 (3%)	0 (0%)
Constipation	1 (1%)	0 (0%)	4 (2%)
Dizziness	1 (1%)	3 (2%)	1 (1%)

Medical Officer Comments: Only adverse events that are regarded by the investigator to be related to the study anti-emetic treatment were reported in this publication. All adverse events experienced by the patients in a clinical trial should have been reported regardless of causality. The severity of adverse events should also be reported.

Beck TM, et al./Hainsworth JD, et al. Study

Two individual reports of this study were identified in the literature. Results reported in each of the study reports were consistent.

J Clin Oncol 1992;10:1969-75

Stratified, Randomized, Double-Blind Comparison of Intravenous Ondansetron Administered as a Multiple-Dose Regimen versus Two Single-Dose Regimens in the Prevention of Cisplatin-Induced Nausea and Vomiting

Semin Oncol 1992;19(6):14-19