

In a trial of 51 pediatric patients (aged 1 month to 24 months) who were undergoing surgery requiring general anesthesia, a single intravenous dose of ondansetron, 0.1 or 0.2 mg/kg, was administered prior to surgery. As shown in Table 6, the 41 patients with pharmacokinetic data were divided into 2 groups, patients aged 1 month to 4 months and patients aged 5 to 24 months, and are compared with pediatric patients aged 3 to 12 years.

Table 6. Pharmacokinetics in Pediatric Surgery Patients Aged 1 Month to 12 Years

Subjects and Age-group	N	CL	V _d	t _{1/2}
		(L/h/kg)	(L/kg)	(h)
Geometric Mean				
Mean				
Pediatric Surgery Patients 3 to 12 years	N = 21	0.439	1.65	2.9
Pediatric Surgery Patients 5 to 24 months	N = 22	0.581	2.3	2.9
Pediatric Surgery Patients 1 month to 4 months	N = 19	0.401	3.5	6.7

In general, surgical and cancer pediatric patients younger than 18 years tend to have a higher ondansetron clearance compared with adults leading to a shorter half-life in most pediatric patients. In patients aged 1 month to 4 months, a longer half-life was observed due to the higher volume of distribution in this age-group.

In a trial of 21 pediatric cancer patients (aged 4 to 18 years) who received three intravenous doses of 0.15 mg/kg of ondansetron at 4-hour intervals, patients older than 15 years exhibited ondansetron pharmacokinetic parameters similar to those of adults.

Patients with Renal Impairment: Due to the very small contribution (5%) of renal clearance to the overall clearance, renal impairment was not expected to significantly influence the total clearance of ondansetron. However, ondansetron mean plasma clearance was reduced by about 41% in patients with severe renal impairment (creatinine clearance < 30 mL/min). This reduction in clearance is variable and was not consistent with an increase in half-life [see *Use in Specific Populations (8.7)*].

Patients with Hepatic Impairment: In patients with mild-to-moderate hepatic impairment, clearance is reduced 2-fold and mean half-life is increased to 11.6 hours compared with 5.7 hours in those without hepatic impairment. In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), clearance is reduced 2-fold to 3-fold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours [see *Dosage and Administration (2.3)*, *Use in Specific Populations (8.6)*].

Drug Interaction Studies
CYP 3A4 Inducers: Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic trial of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, a reduction in AUC, C_{max}, and t_{1/2} of ondansetron was observed. This resulted in a significant increase in the clearance of ondansetron. In a pharmacokinetic study of 10 healthy subjects receiving a single-dose intravenous dose of ondansetron 8 mg after 600 mg rifampin once daily for five days, the AUC and the t_{1/2} of ondansetron were reduced by 48% and 46%, respectively. These changes in ondansetron exposure with CYP3A4 inducers are not thought to be clinically relevant [see *Drug Interactions (7.3)*].

Chemotherapeutic Agents: Carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron [see *Drug Interactions (7.6)*].

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 (approximately 3.6 and 5.4 times the recommended human intravenous dose of 0.15 mg/kg given three times a day, based on BSA). Ondansetron was not mutagenic in standard tests for mutagenicity.

Oral administration of ondansetron up to 15 mg/kg per day (approximately 3.8 times the recommended human intravenous dose, based on BSA) did not affect fertility or general reproductive performance of male and female rats.

14. CLINICAL STUDIES

The clinical efficacy of ondansetron hydrochloride, the active ingredient of Ondansetron Injection, was assessed in clinical trials as described below.

14.1 Chemotherapy-Induced Nausea and Vomiting

Adults
 In a double-blind trial of three different dosing regimens of Ondansetron Injection, 0.015 mg/kg, 0.15 mg/kg, and 0.30 mg/kg, each given three times during the course of cancer chemotherapy, the 0.15-mg/kg dosing regimen was more effective than the 0.015-mg/kg dosing regimen. The 0.30-mg/kg dosing regimen was not shown to be more effective than the 0.15-mg/kg dosing regimen.

Cisplatin-Based Chemotherapy:
 In a double-blind trial in 28 patients, Ondansetron Injection (three 0.15-mg/kg doses) was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin-based chemotherapy. Therapeutic response was as shown in Table 7.

Table 7. Therapeutic Response in Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-day Cisplatin Therapy^a in Adults

	Ondansetron Injection (0.15 mg/kg x 3)	Placebo	P-value ^b
	Number of patients	14	14
Treatment response			
0 Emetic episodes	2 (14%)	0 (0%)	
1-2 Emetic episodes	8 (57%)	0 (0%)	
3-5 Emetic episodes	2 (14%)	1 (7%)	
More than 5 emetic episodes/rescued	2 (14%)	13 (93%)	0.001
Median number of emetic episodes	1.5	Undefined ^c	
Median time to first emetic episode (h)	11.6	2.8	0.001
Median nausea scores (0-100) ^d	3	59	0.034
Global satisfaction with control of nausea and vomiting (0-100) ^e	96	10.5	0.009

^aChemotherapy was high dose (100 and 120 mg/m²); Ondansetron Injection n = 6, placebo n = 5) or moderate dose (50 and 80 mg/m²); Ondansetron Injection n = 8, placebo n = 9). Other chemotherapeutic agents included fluorouracil, doxorubicin, and cyclophosphamide. There was no difference between treatments in the types of chemotherapy that would account for differences in response.
^bEfficacy based on "all-patients-treated" analysis.
^cMedian undefined since at least 50% of the patients were rescued or had more than five emetic episodes.
^dVisual analog scale assessment of nausea: 0 = no nausea, 100 = nausea as bad as it can be.
^eVisual analog scale assessment of satisfaction: 0 = not at all satisfied, 100 = totally satisfied.

Ondansetron injection (0.15-mg/kg x 3 doses) was compared with metoclopramide (2 mg/kg x 6 doses) in a single-blind trial in 307 patients receiving cisplatin \geq 100 mg/m² with or without other chemotherapeutic agents. Patients received the first dose of ondansetron or metoclopramide 30 minutes before cisplatin. Two additional ondansetron doses were administered 4 and 8 hours later, or five additional metoclopramide doses were administered 2, 4, 7, 10, and 13 hours later. Cisplatin was administered over a period of 3 hours or less. Episodes of vomiting and retching were tabulated over the period of 24 hours after cisplatin. The results of this trial are summarized in Table 8.

Table 8. Therapeutic Response in Prevention of Vomiting Induced by Cisplatin (\geq 100 mg/m²) Single-day Therapy^a in Adults

	Ondansetron Injection (0.15 mg/kg x 3)	Metoclopramide 2 mg/kg x 6	P-value
	Number of patients in efficacy population	136	138
Treatment response			
0 Emetic episodes	54 (40%)	41 (30%)	
1-2 Emetic episodes	34 (25%)	30 (22%)	
3-5 Emetic episodes	19 (14%)	18 (13%)	
More than 5 emetic episodes/rescued	29 (21%)	49 (36%)	
Comparison of treatments with respect to			
0 Emetic episodes	54/136	41/138	0.083
More than 5 emetic episodes/rescued	29/136	49/138	0.009
Median number of emetic episodes	1	2	0.005
Median time to first emetic episode (h)	20.5	4.3	< 0.001
Global satisfaction with control of nausea and vomiting (0-100) ^b	85	63	0.001
Acute dystonic reactions	0	8	0.005
Akathisia	0	10	0.002

^aIn addition to cisplatin, 68% of patients received other chemotherapeutic agents, including cyclophosphamide, etoposide, and fluorouracil. There was no difference between treatments in the types of chemotherapy that would account for differences in response.
^bVisual analog scale assessment of satisfaction: 0 = not at all satisfied, 100 = totally satisfied.

Cyclophosphamide-Based Chemotherapy:

In a double-blind, placebo-controlled trial of Ondansetron Injection (three 0.15-mg/kg doses) in 20 patients receiving cyclophosphamide (500 to 600 mg/m²) chemotherapy, Ondansetron Injection was significantly more effective than placebo in preventing nausea and vomiting. The results are summarized in Table 9.

Table 9. Therapeutic Response in Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-day Cyclophosphamide Therapy^a in Adults

	Ondansetron Injection (0.15 mg/kg x 3)	Placebo	P-value ^b
	Number of patients	10	10
Treatment response			
0 Emetic episodes	7 (70%)	0 (0%)	0.001
1-2 Emetic episodes	0 (0%)	2 (20%)	
3-5 Emetic episodes	2 (20%)	4 (40%)	
More than 5 emetic episodes/rescued	1 (10%)	4 (40%)	0.131
Median number of emetic episodes	0	4	0.008
Median time to first emetic episode (h)	Undefined ^c	8.79	
Median nausea scores (0-100) ^d	0	60	0.001
Global satisfaction with control of nausea and vomiting (0-100) ^e	100	52	0.008

^aChemotherapy consisted of cyclophosphamide in all patients, plus other agents, including fluorouracil, doxorubicin, methotrexate, and vincristine. There was no difference between treatments in the type of chemotherapy that would account for differences in response.
^bEfficacy based on "all-patients-treated" analysis.
^cMedian undefined since at least 50% of patients did not have any emetic episodes.
^dVisual analog scale assessment of nausea: 0 = no nausea, 100 = nausea as bad as it can be.
^eVisual analog scale assessment of satisfaction: 0 = not at all satisfied, 100 = totally satisfied.

Re-treatment: In uncontrolled trials, 127 patients receiving cisplatin (median dose, 100 mg/m²) and ondansetron who had two or fewer emetic episodes were re-treated with ondansetron and chemotherapy, mainly cisplatin, for a total of 269 re-treatment courses (median: 2; range: 1 to 10). No emetic episodes occurred in 160 (59%), and two or fewer emetic episodes occurred in 217 (81%) re-treatment courses.

Pediatrics

Four open-label, noncomparative (one US, three foreign) trials have been performed with 209 pediatric cancer patients aged 4 to 18 years given a variety of cisplatin or noncisplatin regimens. In the three foreign trials, the initial dose of Ondansetron Injection ranged from 0.04 to 0.87 mg/kg for a total dose of 2.16 to 12 mg. This was followed by the oral administration of ondansetron ranging from 4 to 24 mg daily for 3 days. In the US trial, Ondansetron Injection was administered intravenously (only) in three doses of 0.15 mg/kg each for a total daily dose of 7.2 to 39 mg. In these trials, 58% of the 196 evaluable patients had a complete response (no emetic episodes) on Day 1. Thus, prevention of vomiting in these pediatric patients was essentially the same as for patients older than 18 years.

An open-label, multicenter, noncomparative trial has been performed in 75 pediatric cancer patients aged 6 to 48 months receiving at least one moderately or highly emetogenic chemotherapeutic agent. Fifty-seven percent (57%) were females; 67% were white, 18% were American Hispanic, and 15% were black patients. Ondansetron Injection was administered intravenously over 15 minutes in three doses of 0.15 mg/kg. The first dose was administered 30 minutes before the start of chemotherapy; the second and third doses were administered 4 and 8 hours after the first dose, respectively. Eighteen patients (25%) received routine prophylactic dexamethasone (i.e., not given as rescue). Of the 75 evaluable patients, 56% had a complete response (no emetic episodes) on Day 1. Thus, prevention of vomiting in these pediatric patients was comparable to the prevention of vomiting in patients aged 4 years and older.

14.2 Prevention of Postoperative Nausea and/or Vomiting

Adults

Adult surgical patients who received ondansetron immediately before the induction of general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or vecuronium or atracurium; and supplemental isoflurane) were evaluated in two double-blind US trials involving 554 patients. Ondansetron Injection (4 mg) intravenous given over 2 to 5 minutes was significantly more effective than placebo. The results of these trials are summarized in Table 10.

Table 10. Therapeutic Response in Prevention of Postoperative Nausea and/or Vomiting in Adult Patients

	Ondansetron 4 mg Intravenous	Placebo	P-value
	Study 1		
Emetic episodes:			
Number of patients	136	139	
Treatment response over 24-h postoperative period			
0 Emetic episodes	103 (76%)	64 (46%)	< 0.001
1 Emetic episode	13 (10%)	17 (12%)	
More than 1 emetic episode/rescued	20 (15%)	58 (42%)	
Nausea assessments:			
Number of patients	134	136	
No nausea over 24-h postoperative period	56 (42%)	39 (29%)	
Study 2			
Emetic episodes:			
Number of patients	136	143	
Treatment response over 24-h postoperative period			
0 Emetic episodes	85 (63%)	63 (44%)	0.002
1 Emetic episode	16 (12%)	29 (20%)	
More than 1 emetic episode/rescued	35 (26%)	51 (36%)	
Nausea assessments:			
Number of patients	125	133	
No nausea over 24-h postoperative period	48 (38%)	42 (32%)	

The populations in Table 10 consisted mainly of females undergoing laparoscopic procedures.

In a placebo-controlled trial conducted in 468 males undergoing outpatient procedures, a single 4-mg intravenous ondansetron dose prevented postoperative vomiting over a 24-hour period in 79% of males receiving drug compared with 63% of males receiving placebo ($P < 0.001$).

Two other placebo-controlled trials were conducted in 2,792 patients undergoing major abdominal or gynecological surgeries to evaluate a single 4-mg or 8-mg intravenous ondansetron dose for prevention of postoperative nausea and vomiting over a 24-hour period. At the 4-mg dosage, 59% of patients receiving ondansetron versus 45% receiving placebo in the first trial ($P < 0.001$) and 41% of patients receiving ondansetron versus 30% receiving placebo in the second trial ($P = 0.001$) experienced no emetic episodes. No additional benefit was observed in patients who received intravenous ondansetron 8 mg compared with patients who received intravenous ondansetron 4 mg.

Pediatrics

Three double-blind, placebo-controlled trials have been performed (one US, two foreign) in 1,049 male and female patients (aged 2 to 12 years) undergoing general anesthesia with nitrous oxide. The surgical procedures included tonsillectomy with or without adenoidectomy, strabismus surgery, herniorrhaphy, and orchidopexy. Patients were randomized to either single intravenous doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo. Study drug was administered over at least 30 seconds, immediately prior to or following anesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these trials are summarized in Table 11.

Table 11. Therapeutic Response in Prevention of Postoperative Nausea and/or Vomiting in Pediatric Patients Aged 2 to 12 Years

	Ondansetron n (%)	Placebo n (%)	P-value
	Study 1		
Number of patients	205	210	
0 Emetic episodes	140 (68%)	82 (39%)	\leq 0.001
Failure ^a	65 (32%)	128 (61%)	
Study 2			
Number of patients	112	110	
0 Emetic episodes	68 (61%)	38 (35%)	\leq 0.001
Failure ^a	44 (39%)	72 (65%)	

Table 11. Therapeutic Response in Prevention of Postoperative Nausea and/or Vomiting in Pediatric Patients Aged 2 to 12 Years (Continued)

Treatment Response Over 24 Hours	Ondansetron n (%)	Placebo n (%)	P-value
Study 3			
Number of patients	206	206	
0 Emetic episodes	123 (60%)	96 (47%)	\leq 0.01
Failure ^a	83 (40%)	110 (53%)	
Nausea assessments^b			
Number of patients	185	191	\leq 0.01
None	119 (64%)	99 (52%)	

^aFailure was one or more emetic episodes, rescued, or withdrawn.

^bNausea measured as none, mild, or severe.

A double-blind, multicenter, placebo-controlled trial was conducted in 670 pediatric patients aged 1 month to 24 months who were undergoing routine surgery under general anesthesia. Seventy-five percent (75%) were males; 64% were white, 15% were black, 13% were American Hispanic, 2% were Asian, and 6% were "other race" patients. A single 0.1-mg/kg intravenous dose of ondansetron administered within 5 minutes following induction of anesthesia was statistically significantly more effective than placebo in preventing vomiting. In the placebo group, 28% of patients experienced vomiting compared with 11% of subjects who received ondansetron ($P \leq 0.01$). Overall, 32 (10%) of placebo patients and 18 (5%) of patients who received ondansetron received antiemetic rescue medication(s) or prematurely withdrew from the trial.

14.3 Prevention of Further Postoperative Nausea and/or Vomiting

Adults

Adult surgical patients receiving general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or vecuronium or atracurium; and supplemental isoflurane) who received prophylactic antiemetics and who experienced nausea and/or vomiting within 2 hours postoperatively were evaluated in two double-blind US trials involving 441 patients. Patients who experienced an episode of postoperative nausea and/or vomiting were given Ondansetron Injection (4 mg) intravenously over 2 to 5 minutes, and this was significantly more effective than placebo. The results of these trials are summarized in Table 12.

Table 12. Therapeutic Response in Prevention of Further Postoperative Nausea and/or Vomiting in Adult Patients

	Ondansetron 4 mg Intravenous	Placebo	P-value
	Study 1		
Emetic episodes:			
Number of patients	104	117	
Treatment response 24 h after study drug			
0 Emetic episodes	49 (47%)	19 (16%)	< 0.001
1 Emetic episode	12 (12%)	9 (8%)	
More than 1 emetic episode/rescued	43 (41%)	89 (76%)	
Median time to first emetic episode (min) ^a	55.0	43.0	
Nausea assessments:			
Number of patients	98	102	
Mean nausea score over 24-h postoperative period ^b	1.7	3.1	
Study 2			
Emetic episodes:			
Number of patients	112	108	
Treatment response 24 h after study drug			
0 Emetic episodes	49 (44%)	28 (26%)	0.006
1 Emetic episode	14 (13%)	3 (3%)	
More than 1 emetic episode/rescued	49 (44%)	77 (71%)	
Median time to first emetic episode (min) ^a	60.5	34.0	
Nausea assessments:			
Number of patients	105	85	
Mean nausea score over 24-h postoperative period ^b	1.9	2.9	

^aAfter administration of study drug.

^bNausea measured on a scale of 0-10 with 0 = no nausea, 10 = nausea as bad as it can be.

The populations in Table 12 consisted mainly of women undergoing laparoscopic procedures.

Repeat Dosing in Adults: In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, intravenous dose of ondansetron 4 mg, administration of a second intravenous dose of ondansetron 4 mg postoperatively does not provide additional control of nausea and vomiting.

Pediatrics

One double-blind, placebo-controlled, US trial was performed in 351 male and female outpatients (aged 2 to 12 years) who received general anesthesia with nitrous oxide and no prophylactic antiemetics. Surgical procedures were unrestricted. Patients who experienced two or more emetic episodes within 2 hours following discontinuation of nitrous oxide were randomized to either single intravenous doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo administered over at least 30 seconds.

Ondansetron was significantly more effective than placebo in preventing further episodes of nausea and vomiting. The results of the trial are summarized in Table 13.

Table 13. Therapeutic Response in Prevention of Further Postoperative Nausea and/or Vomiting in Pediatric Patients Aged 2 to 12 Years

Treatment Response Over 24 Hours	Ondansetron n (%)	Placebo n (%)	P-value
Number of patients	180	171	
0 Emetic episodes	96 (53%)	29 (17%)	\leq 0.001
Failure ^a	84 (47%)	142 (83%)	

^aFailure was one or more emetic episodes, rescued, or withdrawn.

16. HOW SUPPLIED/STORAGE AND HANDLING

Ondansetron Injection, USP 2 mg/mL is available as:

Product Code	Unit of Sale	Strength	Each
RF796320	NDC 76045-216-20 Unit of 24	4 mg/2 mL (2 mg/mL)	NDC 76045-216-00 2 mL Prefilled Disposable Single Use Syringe This product contains an RFID.
796320	NDC 76045-103-20 Unit of 24	4 mg/2 mL (2 mg/mL)	NDC 76045-103-00 2 mL Prefilled Disposable Single Use Syringe

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Product may also be stored in a refrigerator 2°C to 8°C (36°F to 46°F).

Protect from light.

DO NOT DILUTE FOR IV PUSH.