For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

VOMILIFE 4 MG MD

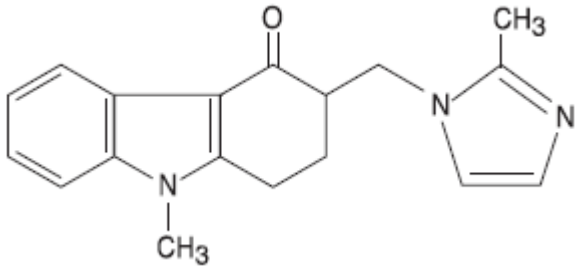
(Ondansetron Orally Disintegrating Tablets)

COMPOSITION

Each uncoated orally disintegrating tablet contains:
Ondansetron I.P. 4 mg
Excipients q.s.
Color: Lake of Sunset Yellow

DESCRIPTION

The active ingredient in Vomilife 4mg MD orally disintegrating tablets is ondansetron base, the racemic form of ondansetron, and a selective blocking agent of the serotonin 5-HT3 receptor type. Chemically it is (±) 1, 2, 3, 9- tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one.It has the following structural formula:



The empirical formula is $C_{18}H_{19}N3_O$ representing a molecular weight of 293.4. Orally Disintegrating tablet formulation is for oral administration of active ingredient (ondansetron) which rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Ondansetron is a selective 5-HT_3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT_3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-HT_{AA} (5-hydroxyindoleacetic acid) excretion increases after cisplatin administration in parallel with the onset of emesis. The released serotonin may stimulate the vagal afferents through the 5-HT_3 receptors and initiate the vomiting reflex. It is reported that, in animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT_3 receptor antagonist while, in healthy volunteers, at single IV 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.

Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

Ondansetron does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anesthetics have not been reported.

PHARMACOKINETICS

Peak plasma concentrations of ondansetron occur about 1.5 hours after an oral dose of 8 mg, and about 6 hours after a rectal dose. The absolute bioavailability is about 60%, mainly because of hepatic first-pass metabolism. In elderly subjects, bioavailability may be somewhat higher (65%) and clearance lower, presumably due to reduced hepatic first – pass metabolism. Ondansetron is extensively distributed in the body; about 70 to 75% of the drug in plasma is protein bound.It is metabolised in the liver through multiple enzymatic pathways; ondansetron is a substrate for cytochrome P450 isoenzymes, primarily CYP3A4, but also CYP1A2 and CYP2D6. Less than 5% of a dose is excreted unchanged in the urine. The terminal elimination half-life is about 3 hours after oral or parenteral doses, and about 6 hours after rectal use.

The terminal elimination half-life is prolonged to about 5 hours in the elderly and in those with renal impairment. These differences are not considered sufficient to warrant dosage adjustment. However, in patients with severe hepatic impairment, bioavailability may approach 100% and clearance is markedly reduced, with elimination half-lives of 15 to 32 hours; dosage restriction is advisable.

Ondansetron systemic exposure does not increase proportionately to dose. Bioavailability is also slightly enhanced by the presence of food but unaffected by antacids. In humans, it is reported that carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron. It is not known whether gender-related differences were clinically important.

Children and Adolescents (aged 1 month to 17 years)

In general, children have a higher clearance than adults, although age-related reductions in clearance have also been reported, with younger children having lower clearances. Use of weight-based doses compensates for these changes and normalises exposure in paediatric patients.

Renal impairment

In patients with renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4h) was reported. A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) reported ondansetron's pharmacokinetics to be essentially unchanged following IV administration.

Elderly or renal impairment

Specific studies in the elderly or patients with renal impairment have been limited to IV and oral administration.

Hepatic impairment
Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. The pharmacokinetics of ondansetron following administration as a suppository has not been reported in patients with hepatic impairment.

INDICATIONS
For Chemotherapy induced nausea and vomiting.

DOSAGES AND ADMINISTRATION
Place Ondansetron orally disintegrating tablet on top of the tongue, where it will disperse within seconds, then swallow.

Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer Chemotherapy
The recommended adult oral dosage of Ondansetron tablet is 24 mg given as six 4 mg tablets administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin $\geq$ 50 mg/m^2. Multiday, singledose admini- stration of a 24 mg dosage has not been studied.

Pediatric Use
There is no experience with the use of a 24 mg dosage in pediatric patients.

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

Prevention of Nausea and Vomiting Associated With Moderately Emetogenic Cancer Chemotherapy
The recommended adult oral dosage is two Ondansetron Tablets given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. Two Ondansetron tablets should be administered twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.

Pediatric Use
For pediatric patients 12 years of age and older, the dosage is the same as for adults. For pediatric patients 4 through 11 years of age, the dosage is one Ondansetron Tablet given 3 times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One Ondansetron tablet should be administered 3 times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

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

Prevention of Nausea and Vomiting Associated With Radiotherapy, Either Total Body Irradiation, or Single High- Dose Fraction or Daily Fractions to the Abdomen

The recommended oral dosage is two Ondansetron Tablets given 3 times a day. For total body irradiation, two Ondansetron Tablets should be administered 1 to 2 hours before each fraction of radiotherapy administered each day.

For single high-dose fraction radiotherapy to the abdomen, two Ondansetron Tablets should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.

For daily fractionated radiotherapy to the abdomen, two Ondansetron Tablets should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each-day radiotherapy is given.

Pediatric Use: There is no experience with the use of Ondansetron Tablets in the prevention of radiation-induced nausea and vomiting in pediatric patients.

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

Postoperative Nausea and Vomiting
The recommended dosage is 16 mg given as four Ondansetron Tablets 1 hour before induction of anesthesia.

Pediatric Use: There is no experience with the use of Ondansetron Tablets in the prevention of postoperative nausea and vomiting in pediatric patients.

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

Dosage Adjustment for Patients with Impaired Renal Function
The dosage recommendation is the same as for the general population. There is no experience beyond first-day administration of ondansetron.

Dosage Adjustment for Patients with Impaired Hepatic Function
In patients with severe hepatic impairment (Child-Pugh 2 score of 10 or greater), clearance is reduced and apparent volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a total daily dose of 8 mg should not be exceeded.

CONTRAINDICATION

Hypersensitivity to any component of the preparation. The concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.

WARNINGS

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists.

ECG changes including QT interval prolongation has been seen in patients receiving ondansetron. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid Ondansetron Orally Disintegrating Tablets in patients with congenital long QT syndrome. ECG monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation.

Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of ondansetron alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Palonosetron and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Palonosetron and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Palonosetron is used concomitantly with other serotonergic drugs.

PRECAUTIONS

General:

Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distension.

Information for Patients:

Phenylketonurics: Phenylketonuric patients should be informed that Ondansetron Orally Disintegrating Tablets contain phenylalanine (a component of aspartame). Each 4-mg and 8-mg orally disintegrating tablet contains < 0.03 mg phenylalanine.

Patients should be instructed not to remove Ondansetron Orally Disintegrating Tablets from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should be gently removed and immediately placed on the tongue to dissolve and be swallowed with the saliva. Peelable illustrated stickers are affixed to the product carton that can be provided with the prescription to ensure proper use and handling of the product.

Drug Interactions: Ondansetron does not itself appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver. Because ondansetron 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. On the basis of available data, no dosage adjustment is recommended for patients on these drugs.

Apomorphine: Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, concomitant use of apomorphine with ondansetron is contraindicated.

Phenytoin, Carbamazepine, and Rifampicin: 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.

Tramadol: Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small studies indicate that ondansetron may be associated with an increase in patient controlled administration of tramadol.

Chemotherapy: Tumor response to chemotherapy in the P-388 mouse leukemia model is not affected by ondansetron. In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover study in 76 pediatric patients, I.V. ondansetron did not increase blood levels of high-dose methotrexate. **Use in Surgical Patients:** The coadministration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

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/day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg/day did not affect fertility or general reproductive performance of male and female rats.

USE IN SPECIFIC POPULATION
Pregnancy:
Teratogenic Effects:

Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, 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.

Nursing Mothers:
Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing woman.

Pediatric Use: Little information is available about dosage in pediatric patients 4 years of age or younger.

Geriatric Use: Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting in US- and foreign-controlled clinical trials, for which there were subgroup analyses, 938 were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of 65.

ADVERSE EVENTS

Chemotherapy-Induced Nausea and Vomiting:

The adverse events in Table 5 have been reported in ≥ 5% of adult patients receiving a single 24-mg Ondansetron tablets in 2 trials. These patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens (cisplatin dose ≥ 50 mg/m^2).

Principal Adverse Events: Single Day Therapy with 24-mg Ondansetron Tablets (Highly Emetogenic Chemotherapy)

Event	Ondansetron 24 mg q.d. n = 300	Ondansetron 8 mg b.i.d. n = 124	Ondansetron 32 mg q.d. n = 117
Headache	33 (11%)	16 (13%)	17 (15%)
Diarrhea	13 (4%)	9 (7%)	3 (3%)

The adverse events in Table 6 have been reported in ≥ 5% of adults receiving either 8 mg of Ondansetron Tablets 2 or 3 times a day for 3 days or placebo in 4 trials. These patients were receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based regimens.

Principal Adverse Events: 3 Days of Therapy with 8-mg Ondansetron Tablets (Moderately Emetogenic Chemotherapy)

Event	Ondansetron 8 mg b.i.d. n = 242	Ondansetron 8 mg t.i.d. n = 415	Placebo n = 262
Headache	58 (24%)	113 (27%)	34 (13%)

Malaise/fatigue	32 (13%)	37 (9%)	6 (2%)
Constipation	22 (9%)	26 (6%)	1 (<1%)
Diarrhea	15 (6%)	16 (4%)	10 (4%)
Dizziness	13 (5%)	18 (4%)	12 (5%)

Central Nervous System:
There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron.

Hepatic:
In 723 patients receiving cyclophosphamide-based chemotherapy in US clinical trials, AST and/or ALT values have been reported to exceed twice the upper limit of normal in approximately 1% to 2% of patients receiving Ondansetron Orally Disintegrating Tablets. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur. The role of cancer chemotherapy in these biochemical changes cannot be clearly determined.

There have been reports of liver failure and death in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

Integumentary:
Rash has occurred in approximately 1% of patients receiving ondansetron.

Other:
Rare cases of anaphylaxis, bronchospasm, tachycardia, angina (chest pain), hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures have been reported. Except for bronchospasm and anaphylaxis, the relationship to Ondansetron Orally Disintegrating Tablets was unclear.

Radiation-Induced Nausea and Vomiting:
The adverse events reported in patients receiving Ondansetron Orally Disintegrating Tablets and concurrent radiotherapy were similar to those reported in patients receiving Ondansetron Orally Disintegrating Tablets and concurrent chemotherapy. The most frequently reported adverse events were headache, constipation, and diarrhea.

Postoperative Nausea and Vomiting:
The adverse events in Table 7 have been reported in ≥ 5% of patients receiving Ondansetron Orally Disintegrating Tablets at a dosage of 16 mg orally in clinical trials. With the exception of headache, rates of these events were not significantly different in the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

Frequency of Adverse Events from Controlled Studies with Ondansetron Tablets (Postoperative Nausea and Vomiting)

Adverse Event	Ondansetron 16 mg (n = 550)	Placebo (n = 531)
Wound problem	152 (28%)	162 (31%)
Drowsiness/sedation	112 (20%)	122 (23%)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Bradycardia	32 (6%)	30 (6%)
Shiver(s)	28 (5%)	30 (6%)
Urinary retention	28 (5%)	18 (3%)
Hypotension	27 (5%)	32 (6%)
Pruritus	27 (5%)	20 (4%)

Preliminary observations in a small number of subjects suggest a higher incidence of headache when Ondansetron Orally Disintegrating Tablets are taken with water, when compared to without water.

Observed During Clinical Practice:
In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of oral formulations of Ondansetron Tablets. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to Ondansetron Tablets.

Cardiovascular:
Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported.

General:
Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable ondansetron.

Hepatobiliary:
Liver enzyme abnormalities

Lower Respiratory:
Hiccups

Neurology:

Oculogyric crisis, appearing alone, as well as with other dystonic reactions

Skin:
Urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Special Senses: Eye Disorders:
Cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours.

DRUG ABUSE AND DEPENDENCE
Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

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

In addition to the adverse events listed above, 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 1 patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg of Ondansetron Tablets. 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.

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
Store protected from light and moisture at a temperature not exceeding 30^{o}C.
Keep out of reach of children

PRESENTATION
Vomilife 4mg MD Tablet is available in Strip of 10 tablets.

MARKETED BY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