PRODUCT MONOGRAPH

PrCCP-ONDANSETRON

Ondansetron Tablets
House Standard

4 mg and 8 mg ondansetron (as ondansetron hydrochloride dihydrate)

Antiemetic
(5-HT_3 receptor antagonist)

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PrCCP-ONDANSETRON

(ondansetron hydrochloride dihydrate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablets/ 4 mg and 8 mg ondansetron (as hydrochloride dihydrate)	Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, , magnesium stearate, triacetin, hypromellose (E5), titanium dioxide, ferric oxide yellow

INDICATIONS AND CLINICAL USE

Adults

CCP-ONDANSETRON (ondansetron hydrochloride dihydrate) is indicated for:

- the prevention of nausea and vomiting associated with emetogenic chemotherapy, including high dose cisplatin, and radiotherapy.
- the prevention and treatment of post-operative nausea and vomiting.

Pediatrics (4-18 years of age)

Post-Chemotherapy Induced Nausea and Vomiting

Ondasetron was effective and well tolerated when given to children 4-12 years of age (see DOSAGE AND ADMINISTRATION). CCP-ONDANSETRON is not indicated for the treatment of children 3 years of age or younger.

Post-Radiotherapy Induced Nausea and Vomiting

CCP-ONDANSETRON is not indicated for use in any age group of this population.

Post-Operative Nausea and Vomiting

CCP-ONDANSETRON is not indicated for use in any age group of this population.

Geriatrics (> 65 years of age)

Post-Chemotherapy and Radiotherapy Induced Nausea and Vomiting

Efficacy and tolerance of ondansetron were similar to that observed in younger adults (see DOSAGE AND ADMINISTRATION).

Post-Operative Nausea and Vomiting

Clinical experience in the use of ondansetron in the prevention and treatment of post- operative nausea and vomiting is limited and is not indicated for use in this population.

CONTRAINDICATIONS

- CCP-ONDANSETRON (ondansetron hydrochloride dihydrate) is contraindicated in patients with a history of hypersensitivity to the drug or any components of its formulations. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- 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 AND PRECAUTIONS

Immune

Cross-reactive hypersensitivity has been reported between different 5-HT_3 antagonists. Patients who have experienced hypersensitivity reactions to one 5-HT_3 antagonist have experienced more severe reactions upon being challenged with another drug of the same class. The use of a different 5-HT_3 receptor antagonist is not recommended as a replacement in cases in which a patient has experienced even a mild hypersensitivity type reaction to another 5-HT_3 antagonist.

Cardiovascular

QTc Interval Prolongation: Ondansetron prolongs the QT interval (see ACTION AND CLINICAL PHARMACOLOGY, Electrocardiography). The magnitude of QTc prolongation will depend on the dose and the infusion rate. In addition, post-marketing cases of torsade de pointes have been reported in patients using ondansetron. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to either QT prolongation or electrolyte abnormalities (see DRUG INTERACTIONS). Hypokalemia, hypocalcemia, and hypomagnesemia should be corrected prior to ondansetron administration.

Additional risk factors for torsade de pointes in the general population include, but are not limited to, the following:

- female gender;
- age 65 years or older;
- baseline prolongation of the QT/QTc interval;
- presence of genetic variants affecting cardiac ion channels or regulatory proteins;
- family history of sudden cardiac death at <50 years;
- cardiac disease (e.g., myocardial ischemia or infarction, left ventricular hypertrophy, cardiomyopathy, conduction system disease);
- history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, orrecent conversion from atrial fibrillation);
- bradycardia (<50 beats per minute);
- acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma);
- nutritional deficits (e.g., eating disorders, extreme diets);
- diabetes mellitus; • autonomic neuropathy.

CCP-ONDANSETRON (ondansetron hydrochloride dihydrate) is not effective in preventing motion-induced nausea and vomiting.

Neurologic

Serotonin syndrome/Neuroleptic Malignant Syndrome: Cases of life-threatening serotonin syndrome or neuroleptic malignant syndrome-like events have been reported with 5-HT3 receptor antagonist antiemetics, including ondansetron, when given in combination with other serotonergic and/or neuroleptic drugs. Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhea). As these syndromes may result in potentially life-threatening conditions, treatment should be discontinued if such events occur and supportive symptomatic treatment should be initiated. If concomitant treatment of CCP-ONDANSETRON with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see DRUG INTERACTIONS).

Hepatic/Biliary/Pancreatic

There is no experience in patients who are clinically jaundiced. The clearance of an 8 mg intravenous dose of ondansetron was significantly reduced and the serum half-life significantly prolonged in subjects with severe impairment of hepatic function. In patients with moderate or severe impairment of hepatic function, reductions in dosage are therefore recommended and a total daily dose of 8 mg should not be exceeded. This may be given as a single intravenous or oral dose.

Ondansetron does not itself appear to induce or inhibit the cytochrome P_{450} drug- metabolizing enzyme system of the liver. Because ondansetron is metabolised by hepatic cytochrome P_{450} drug-metabolizing enzymes, 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.

Gastrointestinal

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

Special Populations

Pregnant Women: The safety of ondansetron for use in human pregnancy has not been established. Ondansetron is not teratogenic in animals. However, as animal studies are not always predictive of human response, the use of ondansetron in pregnancy is not recommended.

Nursing Women: Ondansetron is excreted in the milk of lactating rats. It is not known if it is excreted in human milk, however, nursing is not recommended during treatment with ondansetron.

Pediatrics (< 3 years of age): Insufficient information is available to provide dosage recommendations for children 3 years of age or younger.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drugrelated adverse events and for approximating rates.

Ondansetron has been administered to over 2500 patients worldwide in controlled clinical trials and has been well tolerated.

The most frequent adverse events reported in controlled clinical trials were headache (11%) and constipation (4%). Other adverse events include sensations of flushing or warmth (< 1%).

Cardiovascular:
There have been rare reports of tachycardia, angina (chest pain), bradycardia, hypotension, syncope and electrocardiographic alterations.

Central Nervous System:
There have been rare reports of seizures. Movement disorders and dyskinesia have been reported in two large clinical trials of ondansetron at a rate of 0.1 – 0.3%.

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

Eye Disorder:
Rare cases of transient visual disturbances (e.g. blurred vision) have been reported during or shortly after intravenous administration of ondansetron, particularly at rates equal to or greater than 30 mg in 15 minutes.

Hypersensitivity:
Rare cases of immediate hypersensitivity reactions sometimes severe, including anaphylaxis, bronchospasm, urticaria and angioedema have been reported.

Local Reactions:
Pain, redness and burning at the site of injection have been reported.

Metabolic:
There were transient increases of SGOT and SGPT of over twice the upper limit of normal in approximately 5% of patients. These increases did not appear to be related to dose or duration of therapy. 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. There have been rare reports of hypokalemia.

Other:
There have been reports of abdominal pain, weakness and xerostomia.

Post-Market Adverse Drug Reactions
Over 250 million patient treatment days of ondansetron have been supplied since the launch of the product worldwide. The following events have been spontaneously reported during postapproval use of ondansetron, although the link to ondansetron cannot always be clearly established.

The adverse event profiles in children and adolescents were comparable to that seen in adults.

Immune Disorders:
Rare cases of hypersensitivity reactions, sometimes severe (e.g., laryngeal edema, stridor, laryngospasm and cardiopulmonary arrest) have also been reported.

Cardiovascular Disorders:
There have been rare reports (< 0.01%) of myocardial infarction, myocardial ischemia, angina, chest pain with or without ST segment depression, arrhythmias (including ventricular or supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), electrocardiographic alterations (including second degree heart block), palpitations and syncope.

Rarely and predominantly with intravenous ondansetron, transient ECG changes including QTc interval prolongation, Torsade de Pointes, ventricular fibrillation, cardiac arrest, and sudden death have been reported (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Eye Disorder:
There have been very rare cases of transient blindness following ondansetron treatment, generally within the recommended dosing range and predominantly during intravenous administration.

The majority of blindness cases reported resolved within 20 minutes. Although most patients had received chemotherapeutic agents, including cisplatin a few cases of transient blindness occurred following ondansetron administration for the treatment of post-operative nausea or vomiting and in the absence of cisplatin treatment. Some cases of transient blindness were reported as cortical in origin.

Hepatobiliary Disorders:
Occasional asymptomatic increases in liver function tests have been reported.

Nervous System Disorders:
Transient episodes of dizziness (<0.1%) have been reported predominantly during or upon completion of IV infusion of ondansetron.
Uncommon reports (<1%) suggestive of extrapyramidal reactions including oculogyric crisis/dystonic reactions (e.g. oro-facial dyskinesia, opisthotonos, tremor, etc.), movement disorders and dyskinesia have been reported without definitive evidence of persistent clinical sequelae.

Serotonin syndrome and neuroleptic malignant syndrome-like events have been reported with 5-HT_3 receptor antagonist antiemetics, including ondansetron, when given in combination with other serotonergic and/or neuroleptic drugs (see WARNINGS AND PRECAUTIONS, Neurologic**)**.

Respiratory, Thoracic and Mediastinal Disorders: There have also been rare reports of hiccups.

Skin and Subcutaneous Tissue Disorders:
Very rare reports have been received for bullous skin and mucosal reactions, including fatal cases. These reports include toxic skin eruptions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, and have occurred in patients taking other medications that can be associated with bullous skin and mucosal reactions.

DRUG INTERACTIONS

Serious Drug Interactions

Apomorphine (see CONTRAINDICATIONS)

Drug-Drug Interactions

Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, furosemide, tramadol or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P_{450} enzymes: CYP3A4, CYP2D6 and CYP1A2. Despite the multiplicity of metabolic enzymes capable of metabolising ondansetron which can compensate for an increase or decrease in enzyme activity, it was found that patients treated with inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin) demonstrated an increase in oral clearance of ondansetron and a decrease in ondansetron blood concentrations. No effect in ondansetron clearance secondary to enzyme inhibition or reduced activity (e.g. CYP2D6 genetic deficiency) has been identified to date.

QTc-Prolonging Drugs: The concomitant use of ondansetron with another QTc- prolonging drug should be carefully considered to determine that the therapeutic benefit outweighs the potential risk. Drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list.
Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide);
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone);
- Class 1C antiarrhythmics (e.g., flecainide, propafenone);
- antiemetics (e.g., dolasetron, droperidol, chlorpromazine, prochlorperazine);
- tyrosine kinase inhibitors (e.g., vandetanib, sunitinib, nilotinib, lapatinib);
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, ziprasidone);
- antidepressants (e.g., citalopram, fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline);
- opioids (e.g., methadone);
- domperidone
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus);
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin);
- antimalarials (e.g., quinine, chloroquine);
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole);
- histone deacetylase inhibitors (e.g., vorinostat);
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

Drugs that Cause Electrolyte Abnormalities: The use of CCP-ONDANSETRON with drugs that can disrupt electrolyte levels should be avoided. Such drugs include, but not limited to, the following:

- loop, thiazide, and related diuretics;
- laxatives and enemas;

• amphotericin B; • high dose corticosteroids.

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established.

Tramadol: Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

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

Serotonergic Drugs: As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with 5-HT_3 receptor antagonist antiemetic treatment when given in combination with other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, lithium, sibutramine, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone, and pertazocine or St. John's Wort (*Hypericum perforatum*), and with drugs which impair metabolism of serotonin (such as MAOIs, including linezolid (an antibiotic which is a reversible non-selective MAOI),
and methylene blue; See WARNINGS AND PRECAUTIONS, Neurologic)

DOSAGE AND ADMINISTRATION

Dosing Considerations
Ondansetron has a dose dependent QTc prolongation effect.

Note: CCP-ONDANSETRON is not available for the intravenous route of administration. Therefore, when an ondansetron injection is recommended, a product monograph for ondansetron hydrochloride injection should be consulted"

Recommended Dose And Dosage Adjustment
Chemotherapy Induced Nausea and Vomiting:

Use in Adults:
Highly Emetogenic Chemotherapy (*e.g.* regimens containing cisplatin)

Post-chemotherapy:
After the first 24 hours, CCP-ONDANSETRON 8 up to 8 mg may be taken orally every hours for 5 days.

Less Emetogenic Chemotherapy (e.g. regimens containing cyclophosphamide, doxorubicin, epirubicin, fluorouracil and carboplatin)
Initial Dose:
CCP-ONDANSETRON 8 mg orally 1 to 2 hours prior to chemotherapy.
Post-chemotherapy:
CCP-ONDANSETRON 8 mg orally twice daily for up to 5 days.
Use in Children:

Clinical experience of ondansetron for the treatment of Post-Chemotherapy Induced Nausea and Vomiting in children is currently limited, however, ondansetron was effective and well tolerated when given to children 4-12 years of age.

After therapy, CCP-ONDANSETRON 4 mg should be given orally every 8 hours[1] for up to 5 days.

For children 3 years of age and younger, there is insufficient information available to make dosage recommendations, therefore, CCP-ONDANSETRON is not indicated for the treatment of children 3 years of age or younger (see INDICATIONS AND CLINICAL USE).

Use in Elderly:
Oral Formulations:
Efficacy and tolerance in patients aged over 65 years were similar to that seen in younger adults indicating no need to alter oral dosage schedules in this population.

Radiotherapy Induced Nausea and Vomiting:
Use in Adults:
Initial Dose:
CCP-ONDANSETRON 8 mg orally 1 to 2 hours before radiotherapy. Post-radiotherapy:
CCP-ONDANSETRON 8 mg orally every 8 hours[2] for up to 5 days after a course of treatment.

Use in Children:
There is no experience in clinical studies in this population. CCP-ONDANSETRON is not indicated for the prevention and treatment of radiotherapy induced nausea and vomiting in children (see INDICATIONS AND CLINICAL USE).

Use in Elderly:
Efficacy and tolerance in patients aged over 65 years were similar to that seen in younger adults indicating no need to alter dosage schedules in this population.

Post-Operative Nausea and Vomiting:
Use in Adults:
For prevention of post-operative nausea and vomiting CCP-ONDANSETRON may be administered as a single dose of 16 mg given orally one hour prior to anaesthesia.

Use in Children:
There is no experience in the use of ondansetron in the prevention and treatment of post- operative nausea and vomiting in children CCP-ONDANSETRON is not indicated for this use in children (see INDICATIONS AND CLINICAL USE).

Use in Elderly:

[1] The efficacy of twice daily dosage regimens for the treatment of post-chemotherapy emesis has been established only in adult patients receiving less emetogenic chemotherapy. The appropriateness of twice versus three times daily dosage regimens for other patient groups should be based on an assessment of the needs and responsiveness of the individual patient.
[2] The efficacy of twice daily dosage regimens for the treatment of post-chemotherapy emesis has been established only in adult patients receiving less emetogenic chemotherapy. The appropriateness of twice versus three times daily dosage regimens for other patient groups should be based on an assessment of the needs and responsiveness of the individual patient.

There is limited experience in the use of ondansetron in the prevention and treatment of postoperative nausea and vomiting in the elderly CCP-ONDANSETRON is not indicated for this use in the elderly (see INDICATIONS AND CLINICAL USE).

Patients with Renal/Hepatic Impairment:
Use in Patients with Impaired Renal Function:

No alteration of daily dosage, frequency of dosing, or route of administration is required.

Use in Patients with Impaired Hepatic Function:

The clearance of an 8 mg intravenous dose of ondansetron was significantly reduced and the serum half-life significantly prolonged in subjects with severe impairment of hepatic function. In patients with moderate or severe impairment of hepatic function, reductions in dosage are therefore recommended and a total daily dose of 8 mg should not be exceeded. This may be given as a single oral dose.

No studies have been conducted to date in patients with jaundice.

Patients with Poor Sparteine/Debrisoquine Metabolism:
The elimination half-life and plasma levels of a single 8 mg intravenous dose of ondansetron did not differ between subjects classified as poor and extensive metabolisers of sparteine and debrisoquine. No alteration of daily dosage or frequency of dosing is recommended for patients known to be poor metabolisers of sparteine and debrisoquine.

OVERDOSAGE

For management of a suspected drug overdose contact your regional Poison Control Centre.

At present there is little information concerning overdosage with ondansetron. Individual doses of 84 mg and 145 mg and total daily doses as large as 252 mg have been administered with only mild side effects. There is no specific antidote for ondansetron, therefore, in cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate.

The use of Ipecac to treat overdosage with ondansetron is not recommended as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

"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. Neuromuscular abnormalities, autonomic instability, somnolence, and a brief generalized tonic-clonic seizure (which resolved after a dose of benzodiazepine) were observed in a 12-month-old infant who ingested seven or eight 8-mg ondansetron tablets (approximately forty times the recommended 0.1-0.15 mg/kg dose for a pediatric patient). In all instances, the events resolved completely.

Ondansetron prolongs QT interval in a dose-dependent fashion (see ACTION AND CLINCAL PHARMACOLOGY, Pharmacodynamics). ECG monitoring is recommended in cases of overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

CCP-ONDANSETRON (ondansetron hydrochloride dihydrate) is a selective antagonist of the serotonin receptor subtype, 5-HT_3. Its precise mode of action in the control of chemotherapy induced nausea and vomiting is not known.

Cytotoxic chemotherapy and radiotherapy are associated with the release of serotonin (5-HT) from enterochromaffin cells of the small intestine, presumably initiating a vomiting reflex through stimulation of 5-HT_3 receptors located on vagal afferents. Ondansetron may block the initiation of this reflex. Activation of vagal afferents may also cause a central release of serotonin from the chemoreceptor trigger zone of the area postrema, located on the floor of the fourth ventricle. Thus, the antiemetic effect of ondansetron is probably due to the selective antagonism of 5-HT_3 receptors on neurons located in either the peripheral or central nervous systems, or both.

The mechanisms of ondansetron's antiemetic action in post-operative nausea and vomiting are not known.

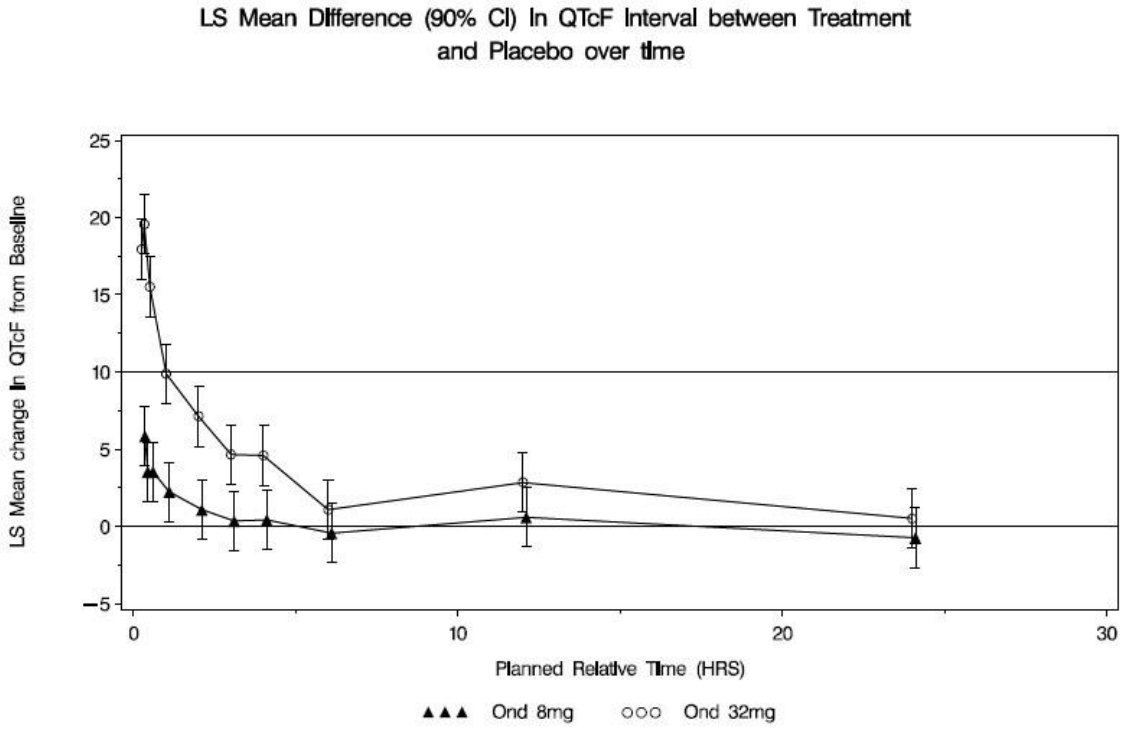
Pharmacodynamics

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P_{450} enzymes, including CYP1A2, CYP2D6 and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolising ondansetron, it is likely that inhibition or loss of one enzyme (e.g. CYP2D6 enzyme deficiency) will be compensated by others and may result in little change in overall rates of ondansetron clearance.

Electrocardiography

The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron was tested at single doses of 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, prolongation of the Fridericia-corrected QTc interval ($QT/RR^{0.33}$=QTcF) was observed from 15 min to 4 h after the start of the 15 min infusion, with a maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction of 19.6 (21.5) msec at 20 min. At the lower tested dose of 8 mg, QTc prolongation was observed from 15 min to 1 h after the start of the 15 minute infusion, with a maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baselinecorrection of 5.8 (7.8) msec at 15 min. The magnitude of QTc prolongation with ondansetron is expected to be greater if the infusion rate is faster than 15 minutes. The 32 mg intravenous dose of ondansetron must not be administered.

No treatment-related effects on the QRS duration or the PR interval were observed at either the 8 or 32 mg dose.



An ECG assessment study has not been performed for orally administered ondansetron. On the basis of pharmacokinetic-pharmacodynamic modelling, an 8 mg oral dose of ondansetron is predicted to cause a mean QTcF increase of 0.7 ms (90% CI -2.1, 3.3) at steady-state, assuming a mean maximal plasma concentration of 24.7 ng/mL (95% CI 21.1, 29.0).

The magnitude of QTc prolongation at the recommended 5 mg/m^2 dose in pediatrics has not been studied, but pharmacokinetic-pharmacodynamic modelling predicts a mean increase of 6.6 ms (90% CI 2.8, 10.7) at maximal plasma concentrations.

Pharmacokinetics

Pharmacokinetic studies in human volunteers showed peak plasma levels of 20-30 ng/mL at around 1½ hours after an 8 mg oral dose of ondansetron. An 8 mg infusion of ondansetron resulted in peak plasma levels of 80-100 ng/mL. Repeat dosing of an 8 mg tablet every 8 hours for 6 days increased the peak plasma value to 40 ng/mL. A continuous intravenous infusion of 1 mg/hour after the initial 8 mg loading dose of ondansetron maintained plasma levels over 30 ng/mL during the following 24 hour period.

The absolute bioavailability of ondansetron in humans was approximately 60% and the plasma protein binding was approximately 73%.

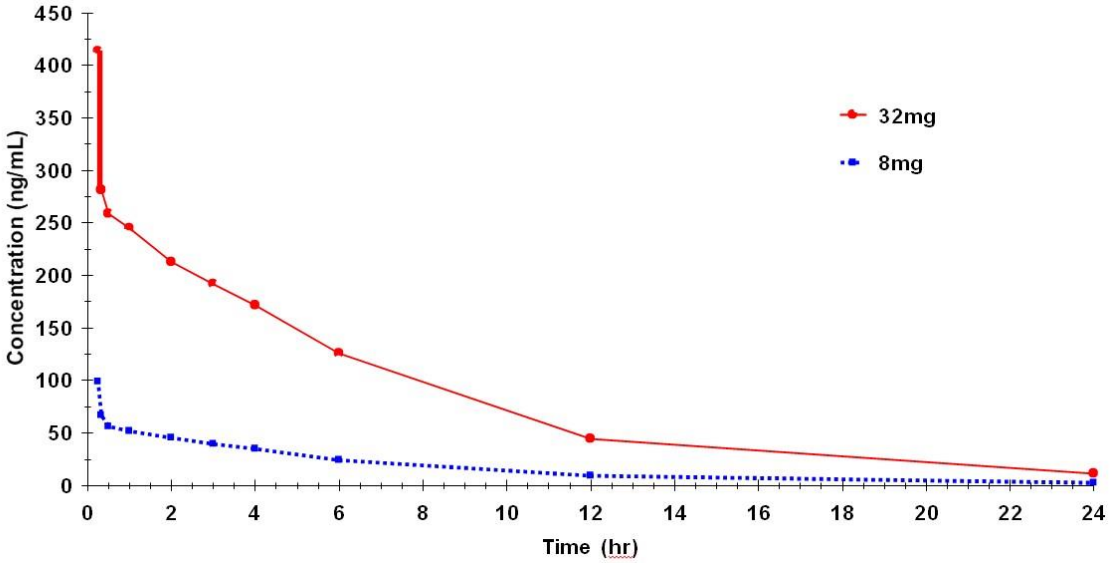
Following oral or IV administration, ondansetron is extensively metabolised and excreted in the urine and faeces. In humans, less than 10% of the dose is excreted unchanged in the urine. The major urinary metabolites are glucuronide conjugates (45%), sulphate conjugates (20%) and hydroxylation products (10%).

The half-life of ondansetron after either an 8 mg oral dose or intravenous dose was approximately 3-4 hours and may be extended to 6-8 hours in the elderly.

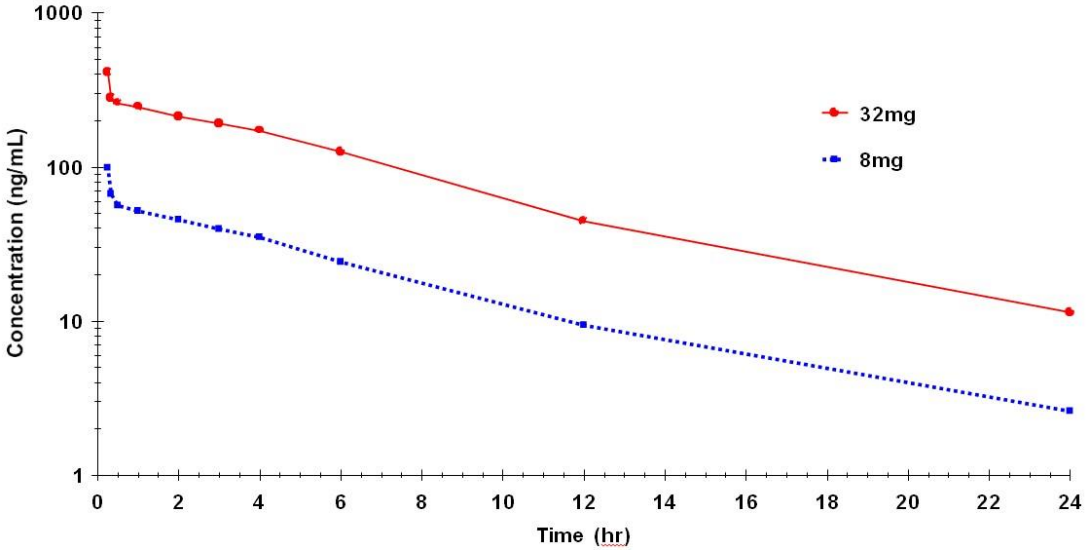
Mean plasma concentration-time curves for ondansetron following 8 mg and 32 mg dose are shown below:

Mean Plasma Concentration-Time Curve for Ondansetron 8mg and 32 mg IV doses

Linear Scale



Semi-logarithmic Scale



In a pharmacokinetic study of 16 epileptic patients maintained chronically on carbamazepine or phenytoin, reduction in AUC, C_{max} and $T_{½}$ of ondansetron was observed. This resulted in a significant increase in clearance. However, on the basis of the inter-subject variability in the available data, no dosage adjustment can be recommended (see DRUG INTERACTIONS – Drug-Drug Interactions).

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials. (See DOSAGE AND ADMINISTRATION, *Use in Elderly*)

Based on more recent ondansetron plasma concentrations and exposure-response modeling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing. (See DOSAGE AND ADMINISTRATION, *Use in Elderly*)

STORAGE AND STABILITY

CCP-ONDANSETRON (ondansetron hydrochloride dihydrate) tablets should be stored between 15 ºC - 30ºC in a dry place.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CCP-ONDANSETRON Tablets 4 mg:
Yellow color, oval, film coated tablets debossed with ‘4’ on one side and “NO” on the other side. Each tablet contains 4 mg of ondansetron (as ondansetron hydrochloride dihydrate) and the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, magnesium stearate, triacetin, hypromellose (E5), titanium dioxide, ferric oxide yellow.
Available in bottle of 30 and 100 tablets unit dose packages of 10 tablets.

CCP-ONDANSETRON Tablets 8 mg:
Yellow color, oval, film coated tablets, debossed with ‘8’ on one side and “NO” on the other side. Each tablet contains 8 mg of ondansetron (as ondansetron hydrochloride dihydrate) and the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, magnesium stearate, triacetin, hypromellose (E5), titanium dioxide, ferric oxide yellow.
Available in bottle of 30 and 100 tablets unit dose packages of 10 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

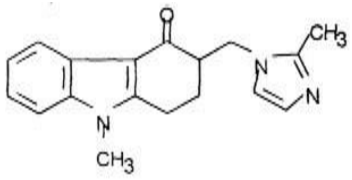
Drug Substance

Proper name: ondansetron hydrochloride dihydrate

Chemical name: 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl) methyl]-4H-carbazol-4-one, hydrochloride dihydrate.

Molecular formula and molecular mass: $C_{18}H_{19}N_3O.HCl.2H_2O$ (hydrochloride dihydrate)
365.9 (hydrochloride hydrate)

Structural formula:



•HCl $2H_2O$

Physicochemical properties:

Description and Solubility:

Ondansetron hydrochloride dihydrate is a white to off-white powder. It is soluble at room temperature in either water (~ 32 mg/mL) or normal saline (~ 8 mg/mL) forming a clear and colourless solution. The melting point of ondansetron hydrochloride dihydrate is about 177° C. pKa is 7.4 and pH of 1% w/v solution in water is approximately 4.6. The distribution coefficient between n-octanol and water is pH dependent:

log D = 2.2 at a pH of 10.60

log D = 0.6 at a pH of 5.95

CLINICAL TRIALS

Comparative Bioavailability Study

An open labelled, randomized, two-treatment, two-period, two-sequence single dose, crossover bioequivalence study of ondansetron hydrochloride 8 mg tablets (CellChem Pharmaceuticals Inc.), compared with Zofran® containing ondansetron hydrochloride 8mg tablets (GlaxoSmithKline Inc., USA) in 24 (+2 stand by) healthy adult, human subjects under fasted conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA (FASTING CONDITIONS)

Ondansetron (one x 8 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Ondansetron*	Zofran†	% Ratio of Geometric Means	90% Confidence Interval**
AUC_T (ng.hr/mL)	225.712 248.841 (44.88)	210.399 229.313 (44.57)	107.28	99.00 - 116.25
AUC_∞ (ng.hr/mL)	233.538 256.740 (44.21)	218.660 236.960 (43.41)	106.80	98.73 - 115.54
C_{max} (ng/mL)	32.154 34.451 (36.96)	31.405 33.788 (41.04)	102.38	94.0 - 111.51
T_{max}§ (hr)	2.19 (30.19)	2.19 (30.56)		
$T_{½}$§ (hr)	6.65 (39.07)	6.48 (31.72)		

* Test product: CCP-Ondansetron , by Cellchem Pharmaceuticals Inc.(manufactured for Cellchem Pharmaceuticals Inc.)

† Reference product: Zofran (GlaxoSmithKline Inc., purchased in USA)

§ Expressed as the arithmetic mean (CV%) only

** Indicates % Confidence Interval (i.e., 90% or 95%) in the column heading and list for the AUC_T, AUC_I and C_{max}

Study results

Clinical trial results showing the number and percentage of patients exhibiting a complete response to ondansetron (0 emetic episodes) are shown in the tables below for both post- operative and chemotherapy induced emesis.

Prevention of Chem otherapy Induced Emesis - Response Over 24 Hours		
Dose	Ondansetron* 3 doses of 0.15 mg/kg	Placebo* 3 doses of placebo
# of patients	14	14
Treatment Response 0 emetic episodes 1-2 emetic episodes	 2 (14%) 8 (57%)	 0 (0%) 0 (0%)

* Results are from an initial study using a different dosing regimen.

Prevention of Post-Operative Emesis – Response Over 24 Hours*		
	Oral Prevention	
Dose	Ondansetron 16 mg od	Placebo
# of patients	253	250
Treatment Response 0 emetic episodes	126 (50%)	79 (32%)

* The majority of patients included in the prevention and treatment of post-operative nausea and vomiting studies using ondansetron have been adult women receiving balanced anaesthesia for gynaecological surgery.

Prevention of Radiotherapy Induced Emesis – Response Over 24 Hours*			
		Oral Treatment	
Dose	Ondansetron 8 mg PO tid*	Metoclopramide 10 mg PO tid*	p value
# of patients	38	44	
Treatment Response 0 emetic episodes	37 (97%)	20 (45%)	< 0.001

* results from a study of adult male and female patients receiving single high dose radiotherapy (800 to 1,000 cGy) over an anterior or posterior field size of ≥ 80 cm^2 to the abdomen.

* Patients received the first dose of ondansetron 8 mg tablets or metoclopramide (10 mg) 1-2 hours before radiotherapy. If radiotherapy was given in the morning, 2 additional doses of study treatment were given (1 tablet late afternoon and 1 tablet before bedtime). If radiotherapy was given in the afternoon, patients took only 1 further tablet that day before bedtime. Patients continued oral medication on a 3 times a day basis for 3-5 days.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics:

The ferret provides an excellent model for demonstrating the antiemetic action of drugs. Emesis can be induced by antineoplastic drugs or whole body irradiation. Behavioural changes associated with these treatments are noted in these animals and may also provide a parallel for the human experience of nausea.

The antiemetic action of ondansetron has been evaluated in both male and female ferrets given cisplatin (9-10 mg/kg), cyclophosphamide (200 mg/kg) or irradiation (2 and 8 Gy, 250 kV). Intravenous doses of ondansetron (0.1-1 mg/kg) abolished cisplatin-induced emesis for up to 2 hours. In cyclophosphamide-induced emesis, subcutaneous doses of 0.5 mg/kg ondansetron completely eliminated vomiting, significantly reduced retching and delayed the onset of these responses.

The radiation-induced emesis, 0.5 mg/kg ondansetron alone completely and rapidly eliminated retching and vomiting.

The antiemetic effects of ondansetron (0.1 mg/kg) in combination with dexamethasone (2-5 mg/kg) were potentiated in ferrets with cyclophosphamide-induced emesis, compared with ondansetron

alone. Ondansetron with dexamethasone produced a significant reduction in retching (65%) and vomiting (72%).
Serotonin receptors of the 5-HT_3 type are present both peripherally and on vagal nerve terminals. Ondansetron probably acts by preventing activation of these receptors or receptors located in other regions of the central nervous system. Both the peripheral and central nervous systems appear to be involved since both abdominal vagotomy and microinjection of ondansetron and other 5-HT_3 antagonists directly into the area postrema eliminate cisplatininduced emesis, while 5-HT_1-like (methiothepin maleate) and 5-HT_2 (ketanserin) antagonists have no effect.

Ondansetron is highly selective for 5-HT_3 receptors and shows negligible binding to other receptors such as 5-HT_1-like, 5-HT_2, α1 and α2 adrenoceptors, β1 and β2 adrenoceptors, D_1 and D_2 muscarinic, nicotinic, $GABA_A$, H_1 and H_2 receptors.

The pharmacological specificity of ondansetron may explain the observed lack of extrapyramidal side effects often seen following similar therapy with metoclopramide, which preferentially binds to dopamine receptors of the D_2 subtype.

Among its secondary effects, ondansetron has also been shown to cause a dose-dependent increase in the rate of gastric emptying in the guinea pig which is significant at doses of 0.010.1 mg/kg. As gastric stasis is frequently associated with nausea, stimulation of gastric motility may be a beneficial action of ondansetron. In the cat, dog and monkey, ondansetron has little effect on heart rate, blood pressure or ECG at intravenous doses up to 3 mg/kg.

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of hERG potassium channels at clinically relevant concentrations. Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacodynamics – Electrocardiography).

Pharmacokinetics:
In mice, rats, rabbits and dogs dosed at 1 mg/kg orally and/or intravenously, the plasma halflife of ondansetron was less than 1 hour, but the half-lives of its metabolites were significantly longer. Peak plasma concentrations of ondansetron in rats and dogs ranged from 351 to 419 ng/mL for the IV dose and 8 to 15 ng/mL for the oral dose. Plasma levels were linear over a 30 fold dose range. In repeat dose studies there was no apparent accumulation of ondansetron. Ondansetron is almost completely absorbed in animals, and is rapidly metabolized by N- demethylation and hydroxylation of the indole ring, followed by conjugation with glucuronic acid and sulphate. There is significant first-pass metabolism after oral doses.

Ondansetron and its metabolites are rapidly and widely distributed in tissues, reaching higher levels than the corresponding plasma levels. In the rat and dog, ondansetron binds reversibly to tissues containing melanin and elastin. In rats and man, plasma protein binding is about 73%, while it is slightly lower in the dog (60%). Ondansetron and its metabolites cross the blood-brain barrier to only a slight extent.

Human Pharmacology
Pharmacodynamics:
In vivo pharmacodynamic studies have investigated the effects of ondansetron on gastric emptying, small bowel transit time and oesophageal motility.

Both oral (16 mg tid) and intravenous (5-10 mg) doses of ondansetron failed to produce a significant effect on gastric emptying in both healthy volunteers and in patients suffering from delayed gastric emptying. However, in one study intravenous doses of 8 mg did increase gastric emptying in over half the volunteers tested.

Intravenous infusion of either 1 mg or 5 mg ondansetron tended to increase small bowel transit times and single intravenous doses of 10 mg ondansetron have been reported to decrease sphincter pressure in the lower oesophagus in some subjects.

In psychomotor testing ondansetron does not impair performance nor cause sedation.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Acute Toxicity

Single doses of ondansetron up to the LD_{50} in mice and in rats were generally well tolerated. Reactions, including tremor and convulsive behaviour, occurred only at near lethal levels.

Species	**LD_{50} (mg/kg)**	
	Oral	**IV**
Mice	10-30	1.0-2.5 15-20
Rats	100-150	

All deaths resulted from the acute effects of treatment, the observed clinical signs being consistent with the central nervous system effects associated with behavioural depression.
These effects were not associated with any apparent histopathological changes in the brain. No target organ toxicity was identified.

Long term Toxicity

Subacute Toxicity Studies

Species	**Route**	**Dose (mg/kg/day)**	**Duration of Study**	**Results**
Rats	Oral	160	7 weeks	Well tolerated
	IV	12	5 weeks	Well tolerated
Dogs	Oral	7.5-25	5 weeks	Transient post-dosing clinical reactions associated with behavioural depression (at highest dose levels)
	IV	2-8	5 weeks	

Maximum daily dose levels in rats were found to be higher when doses were gradually increased. Identical doses were rapidly lethal to rats not previously exposed to ondansetron. Post-dosing reactions, in both rats and dogs, included ataxia, exophthalmia, mydriasis, tremor and respiratory changes. Increases in liver enzymes (SGPT and SGOT) were noted at high dose levels. Dogs dosed at 6.75 mg/kg/day intravenously exhibited vein irritancy in the form of constriction and thickening, creating resistance to needle penetration. The changes were noted after seven days treatment but were reversed by decreasing the dose concentration.

Chronic Toxicity

Species	Duration	Max. no-effect Dose (mg/kg/day)	Effects
Rat Dog	18 months 12 months	1 12	Usually transient and restricted to highest dose

Carcinogenicity Studies

Species	Route	Dose (mg/kg/day)	Duration of Study	Results
Mice Rats	Oral Oral	1-40 (max. oral dose 30) 1-25 (max. oral dose 10)	2 years 2 years	No treatment related increases in tumour incidence. Proportion of benign/malignant tumours also remained Consistent with the pathological background of the Animals studied.

There was no evidence of a tumourigenic effect of ondansetron in any tissue.

Mutagenicity Studies

No evidence of mutagenicity was observed in microbial mutagen tests using mutant strains of *Salmonella typhimurium, Escherichia coli or Saccharomyces cerevisiae*, with or without a rat-liver post-mitochondrial metabolizing system.

There was also no evidence of damage to genetic material noted in in vitro V-79 mammalian cell mutation studies, *in vitro* chromosome aberration tests using human peripheral lymphocytes, or *in vivo* chromosome aberration assays in mouse bone marrow.

Reproduction and Teratology

Ondansetron was not teratogenic in rats and rabbits at dosages up to the maximum non- convulsive level, (rat: 15 mg/kg/day, rabbit: 30 mg/kg/day). No adverse effects on pregnancy or foetal and post-natal development were detected in rats and no foetal abnormalities were observed in rabbits after oral administration of ondansetron.

A slight maternal toxicity was observed at the highest dose level in intravenous organogenesis (4.0 mg/kg/day) studies in the rabbit. Effects included maternal body weight loss and increased incidence of early foetal death. In a rat fertility study, there was a doserelated decrease in the proportion of surviving pups of the F2 generation; however, the significance of this is unclear.

Administration of ondansetron to pregnant rats and rabbits indicated there was foetal exposure to low levels of ondansetron and its metabolites. Ondansetron is retained in the foetal eye presumably bound to melanin. In rats, the transfer of ondansetron and its metabolites into breast milk was extensive. The concentration of unchanged ondansetron in breast milk was higher than in corresponding plasma samples.

Daily administration of ondansetron at dosages up to 15 mg/kg/day to pregnant rats from day 17 of pregnancy to litter day 22 had no effects on pregnancy of the parental generation or on post-natal development and mating of the F1 generation. Foetal development of the F2 generation was comparable to controls; however, the number of implantations and viable foetuses was reduced in the highest dosage group when compared with controls.

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PART III: CONSUMER INFORMATION

PrCCP-ONDANSETRON

Ondansetron Tablets / House Standard
(ondansetron hydrochloride dihydrate)

This leaflet is part III of a three-part "Product Monograph" published when CCP-ONDANSETRON (ondansetron hydrochloride dihydrate) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CCP-ONDANSETRON. Contact your doctor or pharmacist if you have any questions about the drug.

CCP-ONDANSETRON can only be obtained with a prescription from your doctor.

ABOUT THIS MEDICATION

What the medication is used for:

The name of your medicine is CCP-ONDANSETRON tablets (ondansetron hydrochloride dihydrate). This medicine is one of a group called antiemetics. CCP-ONDANSETRON is used for:

- The prevention of nausea (feeling of sickness) and vomiting during treatment for cancer (chemotherapy and radiotherapy).
- The prevention and treatment of nausea and vomiting after surgery.

What it does:

Treatments such as general anaesthesia, cancer chemotherapy and radio therapy are thought to cause the release of a natural substance (serotonin), which can cause you to feel sick and to vomit. CCP-ONDANSETRON helps to stop this from happening, thus preventing you from vomiting or feeling sick.

When it should not be used:

Do not take CCP-ONDANSETRON if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient (see What the nonmedicinal ingredients are) in CCP-ONDANSETRON.
- if you are taking apomorphine (used to treat Parkinson's disease).

What the medicinal ingredient is:

ondansetron hydrochloride dihydrate.

What the nonmedicinal ingredients are:

CCP-ONDANSETRON tablets contain the following nonmedicinal ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, magnesium stearate, triacetin, hypromellose (E5), titanium dioxide, ferric oxide yellow

What dosage form it comes in:

CCP-ONDANSETRON tablets are supplied in two strengths, one contains 4 mg of ondansetron (as ondansetron hydrochloride dihydrate) and the other contains 8 mg of ondansetron (as ondansetron hydrochloride dihydrate). Your doctor will decide which strength you need.

WARNINGS AND PRECAUTIONS

Before you use CCP-ONDANSETRON talk to your doctor or pharmacist if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient in CCP-ONDANSETRON.
- If you have had an allergic reaction to medicines similar to CCP-ONDANSETRON such as medicines containing *granisetron* or *Palonosetron*.
- You are pregnant or likely to become pregnant.
- You are breast feeding.
- You have liver problems.
- You have signs of intestinal obstruction.
- You have a history of heart problems.

If you experience wheezing and tightness of the chest, heart throbbing, swelling of eyelids, face or lips, or develop a skin rash, skin lumps or hives, **contact your doctor immediately. Do not take any more medicine unless your doctor tells you to do so.**

Serotonin Syndrome is a rare but potentially life-threatening reaction that may occur if you take CCP-ONDANSETRON with certain other medications. It may cause serious changes in how your brain, muscles and digestive system work. Be sure to tell your healthcare professional all the medicines you are taking

INTERACTIONS WITH THIS MEDICATIONS

As with most medicines, interactions with other drugs are possible. To avoid potentially life-threatening reactions tell your healthcare professional about **ALL** the medications you take, including those prescribed by other doctors, vitamins, minerals, natural supplements or alternative medicines. It is important that your doctor knows about all your medications so that you get the best possible treatment.

Tell your doctor if you are taking carbamazepine, phenytoin or rifampicin. If you are taking any medicines containing tramadol CCP-ONDANSETRON may decrease its effectiveness.

Also, make sure you tell your doctor or pharmacist if you are taking:

- Drugs used to treat heart rhythm disorders Other drugs that may disturb heart rhythm
- Antipsychotics
- Antidepressants
- Antibiotics or antifungals
- Opiod analgesics (painkillers)
- Other drugs to treat nausea and vomiting
- Asthma drugs
- Cancer drugs
- Diuretics
- Other drugs that affect serotonin including SSRI*s, SNRI**s, triptans, MAOIs*** (including the antibiotic linezolid and methylene blue), drugs that contains tryptophan, or St. John's Wort.

* SSRI (Selective Serotonin-Reuptake Inhibitors) – used to treat depression or anxiety, e.g. escitalopram, citalopram, fluoxetine, paroxetine, sertraline.

** SNRI (Serotonin Noradrenalin Reuptake Inhibitors) – used to treat depression or anxiety, e.g. duloxetine, venlafaxine, desvenlafaxine.

***MAOIs (Monoamine Oxidase Inhibitors) – used to treat depression, Parkinson's disease, e.g., phenelzine, rasagiline, selegiline.

PROPER USE OF THIS MEDICATION

The label on the container of your medicine should tell you how often to take your medicine and how many doses you should take each time. If not, or if you are not sure, consult your doctor or pharmacist.

Do not take more doses, or take them more often than your doctor prescribes. If, however, you vomit within one hour of taking your medicine, you should take the same amount of medicine again. If vomiting persists, consult your doctor.

Usual dose:

Chemotherapy Induced Nausea and Vomiting

Based on how likely you are to experience nausea and/or vomiting, caused by your cancer treatment, your doctor will tell you the amount you need to take and how frequently.

Adult: You may receive CCP-ONDANSETRON before and/or after chemotherapy. The dose of CCP-ONDANSETRON is between 8 and 24 mg a day (taken orally) for up to 5 days depending on the potential of your chemotherapy treatment to cause you to vomit and/or have nausea.

Children (4 to 12 years): After chemotherapy, take 4 mg orally every 8 hours for up to 5 days.

Radiotherapy Induced Nausea and Vomiting

Adult: Take 8 mg orally 1 to 2 hours before radiotherapy. After therapy, take 8 mg orally every 8 hours for up to 5 days after a course of treatment.

Prevention of Post-Operative Nausea and Vomiting

Adult: Take 16 mg orally one hour before anaesthesia.

If you have a liver problem, your dose may be altered. Please follow the instructions of your doctor.

Overdose:

If you think you have taken too much CCP-Citalopram, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose and do not feel sick, take the next dose when it is due.

If you forget to take your medicine and feel sick or vomit, take a dose as soon as possible.

If your doctor decides to stop the treatment, do not keep any leftover medicine unless your doctor tells you to.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You may experience headaches, a feeling of warmness, flushing or constipation, while taking CCP-ONDANSETRON. Although uncommon, low blood pressure and hiccups have also been reported.

There is no need to stop taking your medicine, but you should tell your doctor about these symptoms at your next visit.

If your nausea (feeling of sickness) or vomiting do not improve while taking CCP-ONDANSETRON, consult your doctor for further advice.

If you feel unwell or have any symptoms that you do not understand, you should contact your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Side Effect / Symptom	Talk with your Doctor or Pharmacist	Stop taking drug and seek immediate emergency assistance
Uncommon		
Heart problems such as fast/slow heartbeat, chest pain		X
Seizures		X
Upward rolling of the eyes, abnormal muscular stiffness/body movements/shaking		X
Rare		
Eye problems such as blurred vision	X	
Immediate allergic reaction and symptoms such as swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate		X
Disturbance in heart rhythm (dizziness, palpitations, fainting)		X
Serotonin Syndrome: Symptoms of Serotonin Syndrome have been observed while taking ondansetron with certain other medications. Symptoms include: • Agitation, confusion, restlessness, hallucination, mood changes, unconsciousness, coma. • Fast heartbeat, changes in blood pressure • Muscle shakes, jerks, twitches or stiffness,		X

Side Effect / Symptom	Talk with your Doctor or Pharmacist	Stop taking drug and seek immediate emergency assistance
overactive reflexes, loss of coordination • Nausea, vomiting, diarrhea, fever, sweating, shivering.		
Very rare		
Eye problems such as temporary blindness	X	
Signs of serious skin reactions (skin rash, redness of the skin, blistering of the lips, eyes or mouth, and skin peeling.)		X

This is not a complete list of side effects. For any unexpected effects while taking CCP-ONDANSETRON, contact your doctor or pharmacist.

HOW TO STORE IT

Keep your medicine in a safe place where children cannot reach it. Your medicine may harm them.

CCP-ONDANSETRON tablets should be stored between 15°C - 30°C in a dry place.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhpmps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Remember: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet does not contain the complete information about your medicine. If any questions remain unanswered or you are not sure about something, you should ask your doctor or pharmacist.

You may want to read this leaflet again. **Please Do Not Throw It Away** until you have finished your medicine.

This leaflet plus the full product monograph, prepared for health professionals can be obtained by contacting CellChem Pharmaceuticals Inc. by:

Phone: 613-216-1277

This leaflet was prepared by CellChem Pharmaceuticals Inc., Ottawa, Ontario K2E 7V7.

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