# PERMITTED DAILY EXPOSURE FOR ONDANSETRON

## 1. OBJECTIVE & SEARCH STRATEGY:

Determination of Health based exposure limits for a residual active substance through the derivation of a safe threshold value like Permitted daily exposure (PDE) or threshold of toxicological concern are used to determine the risk of the active pharmaceutical substance. For determination of PDE, all the available pharmacological and toxicological data including both non-clinical and clinical data should be evaluated. This involves hazard identification by reviewing all relevant data, identification of critical effects, determination of NOAEL of the findings that are considered to be critical effects.

In this document, brief summary of pharmacological, pharmacokinetics and toxicity data of Ondansetron have been presented based on the published data. The data were extracted from PubMed, PubChem, TOXLINE, Drugdex, RTECS (Registry of Toxic effects of Chemical Substances), National Toxicology Program (NTP) and FDA.

## 2. INTRODUCTION:

Ondansetron is a medication used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, or surgery. It is also effective for treating gastroenteritis. It has no effect on vomiting caused by motion sickness. It can be given by mouth or by injection into a muscle or into a vein.

Common side effects include diarrhea, constipation, headache, sleepiness, and itchiness. Serious side effects include QT prolongation and severe allergic reaction. It appears to be safe during pregnancy but has not been well studied in this group. It is a serotonin 5-HT3 receptor antagonist. It does not have any effect on dopamine receptors or muscarinic receptors.

## 3. IDENTITY OF THE ACTIVE SUBSTANCE:

Ondansetron is a carbazole derivative with antiemetic activity. As a selective serotonin receptor antagonist, ondansetron competitively blocks the action of serotonin at 5HT3 receptors, resulting in suppression of chemotherapy- and radiotherapy-induced nausea and vomiting. (NCI04)

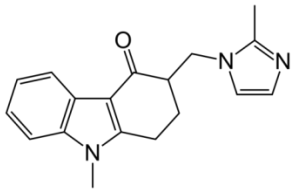
**IUPAC name:** (RS)-9-Methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-2,3-dihydro-1H-carbazol-4(9H)-one

**Chemical Abstract Services (CAS) Registry Number:** 99614-02-5

**Molecular Weight:** 293.4 g/mol g·mol−1

**Chemical Formula:** $C_{18}H_{19}N_3O$

**Molecular Structure:**




## 4. HAZARDS IDENTIFIED:

| CATEGORIZATION: | | | |
|---|---|---|---|
| **TOXICITY** | **YES** | **NO** | **UNKNOWN** |
| **Genotoxicant** | - | √ | - |
| **Carcinogen** | - | √ | - |
| **Reproductive/Developmental Toxicant** | - | √ | - |
| **Highly Sensitizing potential** | - | √ | - |

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| SUMMARY OF HAZARD IDENTIFICATION: | |
|---|---|
| **Pharmacodynamics data** | Ondansetron is a selective 5-HT3 receptor antagonist. While its mechanism of action has not been fully characterized, Ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT3 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-HIAA (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-HT3 receptors and initiate the vomiting reflex. 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-HT3 receptor antagonist. In normal volunteers, single intravenous 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 studied. |
| **Pharmacokinetics data** | Absorption Ondansetron is absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single 8-mg tablet, is approximately 56%. Ondansetron systemic exposure does not increase proportionately to dose. The AUC from a 16-mg tablet was 24% greater than predicted from an 8-mg tablet dose. This may reflect some reduction of first-pass metabolism at higher oral doses. Food Effects: Bioavailability is also slightly enhanced by the presence of food. Distribution Plasma protein binding of ondansetron as measured in vitro was 70% to 76% over the concentration range of 10 to 500 ng/mL. Circulating drug also distributes into erythrocytes. Elimination Metabolism and Excretion: Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The metabolites are observed in the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation. 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 metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination. Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron. |

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## SUMMARY OF HAZARD IDENTIFICATION:

### Acute Toxicity

| Species | Route | End Point | Dose (mg/kg) |
|---|---|---|---|
| Rat | Oral | LD50 | 95 |
| Rat | Para-periosteal | LD50 | 20201 µg/kg |
| Dog | Oral | LD50 | >45 |

| Organism | Test type | Route | Dose | Effect | Reference |
|---|---|---|---|---|---|
| Man | TDLo | Intravenous | 0.229 mg/kg | Liver: jaundice, other or unclassified | Lancet., 344(190), 1994 |
| Rat | LDLo | Intravenous | 20 mg/kg | Null | Seminars in Oncology., 19(Suppl |
| Mouse | LD | Oral | 10 mg/kg | Null | Arzneimittel-Forschung. Drug Research., 46(401), 1996 [PMID:8740088] |
| Mouse | LD | Intraperitoneal | 5 mg/kg | Null | Arzneimittel-Forschung. Drug Research., 46(401), 1996 [PMID:8740088] |
| Mouse | LDLo | Intravenous | 2.5 mg/kg | Null | Seminars in Oncology., 19(Suppl |
| Dog | LD | Intravenous | 10 mg/kg | Null | Seminars in Oncology., 19(Suppl |

### Repeated Dose Toxicity (Chronic Toxicity)

| Duration | Species | Route | Dose (mg/kg/day) | End Point | Effects |
|---|---|---|---|---|---|
| 7 weeks | Rat | Oral | 160 | Maximally tolerated dose | |
| 18 months | Rat | No route specified | 1 | NOAEL | Central Nervous System Liver |
| 12 months | Dog | No route specified | 12 | NOAEL | Central Nervous System Liver |

### Carcinogenicity

| Duration | Species | Route | Dose (mg/kg/day) | End Point | Effects |
|---|---|---|---|---|---|
| 2 Year(s) | Rat | Oral | 10 | NOAEL | Not Carcinogenic |
| 2 Year(s) | Mouse | Oral | 30 | NOAEL | Not Carcinogenic |

Carcinogenic effects were not seen in 2-year studies in rats and mice with oral Ondansetron doses up to 10 mg/kg per day and 30 mg/kg per day, respectively (approximately 4 and 6 times the maximum recommended human oral dose of 24 mg per day, based on body surface area).

### In vivo/In vitro Genotoxicity Studies

| Study type | Cell Type/Organism | Result |
|---|---|---|
| Bacterial Mutagenicity (Ames) | Salmonella , E. coli | Negative |
| In Vitro Chromosome Aberration | Human Lymphocytes | Negative |
| In Vivo Chromosome Aberration | Mouse Bone Marrow | Negative |

Ondansetron was not mutagenic in standard tests for mutagenicity.

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## SUMMARY OF HAZARD IDENTIFICATION:

**Reproductive/Developmental Toxicity**

| Duration | Species | Route | Dose (mg/kg/day) | End Point | Effects |
|---|---|---|---|---|---|
| Reproductive & Fertility | Rat | Oral | 15 | NOAEL | Negative |
| Fertility and Embryonic Development | Rat | i.v. | 4 | NOAEL | No effect at maximum dose |
| Fertility and Embryonic Development | Rabbit | i.v. | 4 | NOAEL | No effect at maximum dose |

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of Ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of Ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area. In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of Ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal exposure margin was approximately 6 times the maximum recommended human oral dose of 24 mg/day, based on body surface area.

**Highly Sensitizing Potential**

A very serious **allergic** reaction to this drug is unlikely.
Symptoms of a serious **allergic** reaction include: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

## IDENTIFICATION OF CRITICAL EFFECTS:

| | |
|---|---|
| **Sensitive Indicator of an adverse effect seen in non-clinical toxicity data** | No any adverse effect seen in non-clinical toxicity data. |
| **Clinical therapeutic and adverse effects** | **Clinical therapeutic dose:**<br>**Recommended dose:** 24 mg orally 30 minutes before the start of single-day HEC (including cisplatin doses of 50 mg/m2 or greater)<br>**Recommended dose:** 16 mg orally 1 hour before the induction of anesthesia<br>**The most common side effects of Ondansetron are:**<br>Headache<br>Fatigue<br>Constipation<br>Diarrhea<br>Dizziness<br>Rash<br>Hiccups<br>Flushing |
| **NOAEL/LOAEL** | Oral repeat dose toxicological studies established the NOAELs of 1 mg/kg/day in rats |

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| APPLICATION OF ADJUSTMENT FACTORS: | | |
|---|---|---|
| **F1:** Extrapolation between species | 5 | For extrapolation from rats to humans. |
| **F2:** Inter Individual Variability | 10 | Used for differences between individuals in the human population. |
| **F3:** Duration of Toxicity (Repeat Dose Toxicity) | 1 | 18 months study for rats. |
| **F4:** Severe Toxicity (1-10) | 1 | No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed |
| **F5:** NOAEL or LOAEL (10 if LOAEL) | 5 | Oral repeat dose toxicological studies established the NOAELs of 1 mg/kg/day in rats |
| **PK Correction** | For PDE calculation no pharmacokinetic correction was carried out | |

| CALCULATION | |
|---|---|
| **PDE Calculation** | $\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$<br>$= \frac{\text{1 (NOAEL) x 50}}{\text{5 x 10 x 1 x 1 x 5}}$<br>= 0.2 mg/day |

## 5. REFERENCES:


- https://en.wikipedia.org/wiki/Ondansetron
- https://pfe-pfizercom-prod.s3.amazonaws.com/products/material_safety_data/PZ00456.pdf
- https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022524Orig1s000MedR.pdf
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020103s030,020605s014,020781s014lbl.pdf
- https://pubchem.ncbi.nlm.nih.gov/compound/Ondansetron.