Valentron 0.25mg/5ml Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT

Valentron 0.25mg/5ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 5ml contains 281mcg of Palonosetron Hydrochloride equivalent to 250mcg of Palonosetron.
For the full list of excipients, see section List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Valentron is indicated in adults for:

Chemotherapy – Induced Nausea and Vomiting

Adults and Paediatric Patients 1 month of Age and Older

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy
- the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Postoperative Nausea and Vomiting

- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

As with other emetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and vomiting must be avoided during the postoperative period, Valentron is recommended even where the incidence of postoperative nausea and/or vomiting is low.

4.2 Posology and method of administration

This medicinal product should be administered by a healthcare professional under appropriate medical supervision.

Posology
Adults
Chemotherapy – Induced Nausea and Vomiting
250 µg palonosetron administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Valentron should be injected over 30 seconds.
The efficacy of Valentron in the prevention of nausea and vomiting induced by highly emetogenic chemotherapy may be enhanced by the addition of a corticosteroid administered prior to chemotherapy.

Postoperative Nausea and Vomiting
75 µg palonosetron administered as a single intravenous bolus over 10 seconds immediately before the induction of anaesthesia.

Paediatric population
Chemotherapy – Induced Nausea and Vomiting
Children and Adolescents (aged 1 month to 17 years):
20 µg/kg (the maximum total dose should not exceed 1500 µg) palonosetron administered as a single 15-minute intravenous infusion beginning approximately 30 minutes before the start of chemotherapy. The safety and efficacy of Valentron in children aged less than 1 month have not been established. No data are available.

Postoperative Nausea and Vomiting
Safety and effectiveness in patients below the age of 18 years have not been established.

Elderly population
No dose adjustment is necessary for the elderly.

Hepatic impairment
No dose adjustment is necessary for patients with impaired hepatic function.

Renal impairment
No dose adjustment is necessary for patients with impaired renal function.
No data are available for patients with end stage renal disease undergoing haemodialysis.

Method of administration
Intravenous

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

As palonosetron may increase large bowel transit time, patients with a history of constipation or signs of subacute intestinal obstruction should be monitored following administration. Two cases of constipation with faecal impaction requiring hospitalisation have been reported in association with palonosetron 750 µg.

At all dose levels tested, palonosetron did not induce clinically relevant prolongation of the QTc interval. However, as for other 5-HT3 antagonists, caution should be exercised in the use of palonosetron in patients who have or are likely to develop prolongation of the QT interval. These conditions include patients with a personal or family history of QT prolongation, electrolyte abnormalities, congestive heart failure, bradyarrhythmias, conduction disturbances and in patients taking anti-arrhythmic agents or other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Hypokalemia and hypomagnesemia should be corrected prior to 5-HT3-antagonist administration. There have been reports of serotonin syndrome with the use of 5-HT3 antagonists either alone or in combination with other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

It should not be used to prevent or treat nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration.

4.5 Interaction with other medicinal products and other forms of interaction

Palonosetron is mainly metabolised by CYP2D6, with minor contribution by CYP3A4 and CYP1A2 isoenzymes. Based on *in vitro* studies, palonosetron does not inhibit or induce cytochrome P450 isoenzyme at clinically relevant concentrations.
Chemotherapeutic agents
Palonosetron did not inhibit the antitumour activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C).

Metoclopramide
No significant pharmacokinetic interaction was shown between a single intravenous dose of palonosetron and steady state concentration of oral metoclopramide, which is a CYP2D6 inhibitor.

CYP2D6 inducers and inhibitors
In a population pharmacokinetic analysis, it has been shown that there was no significant effect on palonosetron clearance when co-administered with CYP2D6 inducers (dexamethasone and rifampicin) and inhibitors (including amiodarone, celecoxib, chlorpromazine, cimetidine, doxorubicin, fluoxetine, haloperidol, paroxetine, quinidine, ranitidine, ritonavir, sertraline or terbinafine).

Corticosteroids
Palonosetron has been administered safely with corticosteroids.

Serotonergic Drugs (e.g. SSRIs and SNRIs)
There have been reports of serotonin syndrome following concomitant use of 5-HT3 antagonists and other serotonergic drugs (including SSRIs and SNRIs).

Other medicinal products
Palonosetron has been administered safely with analgesics, antiemetic/antinauseants, antispasmodics and anticholinergic medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no experience of palonosetron in human pregnancy. Therefore, palonosetron should not be used in pregnant women unless it is considered essential by the physician.

Breast-feeding
As there are no data concerning palonosetron excretion in breast milk, breast-feeding should be discontinued during therapy.

Fertility
There are no data concerning the effect of palonosetron on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
Since palonosetron may induce dizziness, somnolence or fatigue, patients should be cautioned when driving or operating machines.

4.8 Undesirable effects
The following adverse reactions were observed as possibly or probably related to Palonosetron Hydrochloride.

System organ class	Common	Uncommon	Very rare
Immune system disorders			Hypersensitivity, anaphylaxis, anaphylactic/anaphylactoid reactions and shock
Metabolism and nutrition disorders		Hyperkalaemia, metabolic disorders, hypocalcaemia, hypokalaemia, anorexia, hyperglycaemia, appetite decreased	
Psychiatric disorders		Anxiety, euphoric mood	
Nervous system disorders	Headache Dizziness	Somnolence, insomnia, paraesthesia, hypersomnia, peripheral sensory neuropathy	
Eye disorders		Eye irritation, amblyopia	
Ear and labyrinth disorders		Motion sickness, tinnitus	
Cardiac disorders		Tachycardia, bradycardia, extrasystoles, myocardial ischaemia, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles	
Vascular disorders		Hypotension, hypertension, vein discolouration, vein distended	
Respiratory, thoracic and mediastinal disorders		Hiccups	
Gastrointestinal disorders	Constipation Diarrhoea	Dyspepsia, abdominal pain, abdominal pain upper, dry mouth, flatulence	
Hepatobiliary disorders		Hyperbilirubinaemia	
Skin and subcutaneous tissue disorders		Dermatitis allergic, pruritic rash	
Musculoskeletal and connective tissue disorders		Arthralgia	
Renal and urinary disorders		Urinary retention, glycosuria	
General disorders and administrative site conditions		Asthenia, pyrexia, fatigue, feeling hot, influenza like illness	Injection site reaction*
Investigations		Elevated transaminases -, electrocardiogram QT	

System organ class	Common	Uncommon	Very rare
		prolonged	

* Includes the following: burning, induration, discomfort and pain

Paediatric population
The following adverse reactions were evaluated in paediatric patients receiving palonosetron for up to 4 chemotherapy cycles.

System organ class	Common	Uncommon
Nervous system disorders	Headache	Dizziness, dyskinesia
Cardiac disorders		Electrocardiogram QT prolonged conduction disorder, sinus tachycardia
Respiratory, thoracic and mediastinal disorders		Cough, dyspnoea, epistaxis
Skin and subcutaneous tissue disorders		Dermatitis allergic, pruritus, skin disorder, urticaria
General disorders and administration site conditions		Pyrexia, infusion site pain, infusion site reaction, pain

4.9 Overdose

No case of overdose has been reported. In the unlikely event of overdose with Valentron this should be managed with supportive care. Dialysis studies have not been performed, however, due to the large volume of distribution, dialysis is unlikely to be an effective treatment for Valentron overdose.

Paediatric population
No case of overdose has been reported in paediatric.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin ($5HT_3$) antagonists. ATC Code: A04AA05

Palonosetron is a selective high-affinity receptor antagonist of the $5HT_3$ receptor.
The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc was found comparable to ondansetron and dolasetron.

Paediatric population
Prevention of Chemotherapy Induced Nausea and Vomiting (CINV):
Reported efficacy of Palonosetron i.v at single dose of 10 µg/kg compared to 3µg/kg is 54.1 % and 37.1 % respectively. No safety concerns are available at either dose level.
It is also reported that paediatric patients require a higher palonosetron dose than adults to prevent chemotherapy-induced nausea and vomiting, the safety profile is consistent with the established profile in adults.

Prevention of Post Operative Nausea and Vomiting (PONV):
The proportion of patients without emesis during 0-72 hours post operatively was similar after palonosetron 1 µg/kg or 3 µg/kg (88% vs 84%).

5.2 Pharmacokinetic properties

Absorption
Following intravenous administration, an initial decline in plasma concentrations is followed by slow elimination from the body with a mean terminal elimination half-life of approximately 40 hours. Mean maximum plasma concentration (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) are generally dose-proportional over the dose range of 0.3–90 µg/kg.

Distribution
Palonosetron at the recommended dose is widely distributed in the body with a volume of distribution of approximately 6.9 to 7.9 l/kg. Approximately 62 % of palonosetron is bound to plasma proteins.

Biotransformation
Palonosetron is eliminated by dual route, about 40 % eliminated through the kidney and with approximately 50 % metabolised to form two primary metabolites, which have less than 1 % of the $5HT_3$ receptor antagonist activity of palonosetron. CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 isoenzymes are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolisers of CYP2D6 substrates. Palonosetron does not inhibit or induce cytochrome P450 isoenzymes at clinically relevant concentrations.

Elimination
After a single intravenous dose of 10 µg/kg [^{14}C]-palonosetron, approximately 80 % of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40 % of the administered dose, as unchanged active substance. The low total body clearance and large volume of distribution resulted in a terminal elimination half-life in plasma of approximately 40 hours.

Pharmacokinetics in special populations
Elderly people
Age does not affect the pharmacokinetics of palonosetron. No dosage adjustment is necessary in elderly patients.

Gender
Gender does not affect the pharmacokinetics of palonosetron. No dosage adjustment is necessary based on gender.

Paediatric population
When the dose was increased from 10 µg/kg to 20 µg/kg a dose-proportional increase in mean AUC was observed. Following single dose intravenous infusion of palonosetron 20µg/kg, peak plasma concentrations (C_T) reported at the end of the 15 minutes infusion were highly variable in all age groups and tended to be lower in patients < 6 years than in older paediatric patients. Median half-life was 29.5 hours in overall age groups and ranged from about 20 to 30 hours across age groups after administration of 20µg/kg.
The total body clearance (L/h/kg) in patients 12 to 17 years old was similar to that in healthy adults. There are no apparent differences in volume of distribution when expressed as L/kg.

Renal impairment
Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Severe renal impairment reduces renal clearance, however total body clearance in these patients is similar to healthy subjects. No dosage adjustment is necessary in patients with renal insufficiency. No pharmacokinetic data in haemodialysis patients are available.

Hepatic impairment
Hepatic impairment does not significantly affect total body clearance of palonosetron.
While the terminal elimination half-life and mean systemic exposure of palonosetron is increased with

severe hepatic impairment, this does not warrant dose reduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, Disodium edetate, Sodium citrate, Citric acid monohydrate, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment), Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Please refer to the expiry date on the product labels.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

LYO Imp (Tubular) glass vial with bromobutyl siliconised rubber stopper and plastic cap with Aluminium Seal.
Available in packs of 1 vial containing 5ml of solution.

6.6 Special precautions for disposal

Single use only, any unused solution should be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MANUFACTURER

Manufactured by:
USV Private Limited,
H-13, 16,16A,17,18,19,20,21,E-22,
OIDC, Mahatma Gandhi Udyog Nagar,
Dabhel, Daman – 396210, India

PRODUCT REGISTRATION HOLDER
Novugen Pharma Sdn. Bhd.
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Hicom Glenmarie Industrial Park
40150 Shah Alam, Selangor, Malaysia

8 DATE OF REVISION

18/07/2023

Package insert is drafted in Times New Roman with font size of 11, subject to change based on any other legible font and font size.