Summary of Product Characteristics for Pharmaceutical Product

1. Name of the medicinal product

Setonix 1mg/ml Solution for Injection.

2. Qualitative and quantitative composition

Setonix 1mg/1ml Solution for Injection: vial contains 1mg of Granisetron as active substance.
Setonix 3mg/3ml Solution for Injection: vial contains 3mg of Granisetron as active substance.

3. Pharmaceutical form

Solution for injection.

4. Clinical particulars

4.1. Therapeutic indications

Cytostatic chemotherapy:
SETONIX® is used intravenously in adults and children from the age of 2 years for the prevention and treatment of nausea and vomiting due to cytostatic chemotherapy.
Radiotherapy:
In adults SETONIX® is used intravenously for the prophylaxis and treatment of radiotherapy-induced nausea and vomiting.
Postoperative nausea and vomiting:
SETONIX® is used intravenously in adults for the treatment of postoperative nausea and vomiting.

4.2. Posology and method of administration

Standard dosage in adults:
Cytostatic chemotherapy (prophylaxis):
Intravenous:
Patients weighing over 50 kg body weights: 1 vial (3mg) is diluted in 20-50 ml infusion solution and administered over a period of 5 minutes before the cytostatic therapy. This 3 mg dose can also be given as a bolus injection over 30 seconds Vials of 3 mg are supplied for this purpose.
Patients weighing under 50 kg body weights: 20-40 µg/kg body weight, i.e. an appropriate volume of SETONIX® solution (vials of 3 mg/3 ml and 1 mg/1 ml are supplied). The infusion should be completed before the cytostatic therapy is started. The majority of patients require only a single dose to control nausea and vomiting over 24 hours.

Radiotherapy (prophylaxis):
Intravenous: The same dosage recommendations apply as for Cytostatic chemotherapy (prophylaxis).
Cytostatic chemotherapy (intervention):
In the small proportion of patients in whom breakthrough nausea and vomiting occur, up to two additional 5minute infusions of 3 mg, given at least 10 minutes

apart, may be administered within a 24-hour period. The maximum dose is 9 mg/24 hours.
Postoperative nausea and vomiting (intervention):
For the treatment of postoperative nausea and vomiting, a single dose of 1 mg of SETONIX® should be administered by slow intravenous injection (over 30 seconds).
Patients undergoing anesthesia for elective surgery have received total doses of up to 3 mg of SETONIX® intravenously.
Special Populations:
Children:
Cytostatic therapy (prophylaxis):
Intravenous: a single dose of 20 µg/kg body weight, diluted in 10-30 ml infusion solution, should be administered by intravenous infusion 5 minutes before the cytostatic therapy.
Cytostatic therapy (intervention):
Up to two additional 5-minute infusions of 20 µg/kg, given at least 10 minutes apart, may be administered. The maximum dose is 3 times 20 µg/kg per 24-hour period.
Postoperative nausea and vomiting:
No experience is available on the use of Granisetron hydrochloride IV to treat postoperative nausea and vomiting in children.
Geriatrics, liver failure, renal failure:
No dosage adjustment required.

4.3. Contraindications

Known hypersensitivity to Granisetron.
There is evidence of a possible hypersensitivity reaction in patients who have shown a hypersensitivity reaction to other selective 5-HT3 receptor antagonists.

4.4. Special warnings and precautions for use

As SETONIX® may reduce lower bowel motility; patients with signs of subacute intestinal obstruction should be monitored closely following administration of SETONIX®. No special precautions are required in elderly patients or in patients with renal or hepatic impairment. In healthy people, no clinically relevant effects on resting EEG or on the performance of psychometric tests were observed after intravenous administration at any dose tested (up to 200 µg/kg).

4.5. Interaction with other medicinal products and other forms of interaction

The efficacy of SETONIX® may be enhanced by intravenous administration of a single dose of dexamethasone (8-20 mg) before chemotherapy. In In-vitro studies the metabolism of Granisetron was inhibited by ketoconazole. This suggests involvement of a cytochrome P450 3A isoenzyme. Other in-vitro studies have definitively excluded involvement of the cytochrome P450 3A4 subfamily. No specific interaction studies have been conducted in anesthetised patients, but SETONIX® has been safely administered with commonly used anesthetic and analgesic agents.
In-vitro studies have shown that cytochrome P450 3A4, which is involved in the metabolism of the most common narcotic analgesic agents, is not influenced by

Granisetron. In healthy people, hepatic enzyme induction with phenobarbital increased total plasma clearance of intravenous Granisetron by approximately a quarter.

Granisetron has been safely used in humans receiving benzodiazepines, neuroleptics, and anti-ulcer drugs, which are commonly prescribed with anti-emetics. Similarly, no interactions with emetogenic cytostatic drugs been observed.

4.6. pregnancy and lactation

Pregnancy:

Animal experiments have not revealed any teratogenic effects; however, no studies are available on pregnant and lactating women.

Use of SETONIX® should therefore be limited to situations where the potential benefit to the mother justifies the potential risk to the fetus or nursing infant.

Lactation:

There are no data on the excretion of granisetron in breast milk. Women should therefore not breastfeed while receiving SETONIX®.

4.7. Effects on ability to drive and use machines

There are no data on the effects of Granisetron on the ability to drive. Somnolence was occasionally reported, and this should be borne in mind. A relationship to treatment with SETONIX® has not been established.

4.8. Undesirable effects

In most cases, the adverse events seen in association with Granisetron have not been severe and have been tolerated by patients, so that treatment has not had to be stopped.

Rare cases of hypersensitivity reactions have occurred and have sometimes been severe (e.g. anaphylaxis). Immune system:

Rare: hypersensitivity reactions.

Nervous system:

Very frequent: headache (14%).

Cardiovascular system:

Isolated serious adverse events (hypotension, cardiac arrhythmias) have been reported. Gastrointestinal system:

Infrequent: constipation.

Skin and subcutaneous tissue:

Very rare: rash, edema/facial edema.

Body as a whole:

Infrequent: flu-like symptoms including fever and chills. Rare: transient elevation of transaminases.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9. Overdose

There is no specific antidote to Granisetron.

In the event of over dosage, symptomatic treatment should be given.

Over dosage with single intravenous doses of more than 38 mg Granisetron has occurred without symptoms or with only slight headache.

5. Pharmacological properties

5.1. Pharmacodynamics properties

SETONIX® (Granisetron) is a selective 5-HT3 receptor antagonist. Binding studies have demonstrated that Granisetron has negligible affinity for other receptor types including 5-HT and dopamine D2 binding sites. Granisetron suppresses the nausea and vomiting induced by cytostatic therapy or after an operation. The parenteral form of Granisetron can be used either prophylactically or by intervention.
SETONIX® has no effect on plasma levels of prolactin or aldosterone.
Granisetron was found to be non-mutagenic and there was no evidence of unscheduled Granisetron DNA synthesis; these findings indicate that. Granisetron is non-genotoxic. At higher doses, Granisetron induced cell proliferation in the rat liver and hepatocellular tumors in rats and mice treated orally over their lifetime (2 years). Hepatocellular tumors were not observed in 2-year rodent studies at dosages 25 times the intravenous clinical dose. In conclusion, Granisetron was given without harm to rats and dogs for 12 months at substantial multiples of the clinical dose.
The finding of an increase in hepatocellular tumors in rodents given high dose of the drug over their lifetime is not considered to represent a hazard for short-term use of SETONIX® as an antiemetic in humans.

5.2 Pharmacokinetic properties

Distribution: Granisetron is distributed throughout the body, with a mean volume of distribution of 3 l/kg. Plasma protein binding is approximately 65%.

Metabolism: Biotransformation occurs principally via N-demethylation and aromatic ring oxidation followed by conjugation. In in-vitro studies the metabolism of Granisetron was inhibited by ketoconazole. This suggests involvement of a cytochrome P450 3A isoenzyme. Other in-vitro studies have definitively excluded involvement of the cytochrome P450 3A4 subfamily.
Elimination: Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged Granisetron averages 12% and that of metabolites 47% of dose. The remaining 41% is excreted in the feces as metabolites. Mean plasma half- life in patients after intravenous administration is 9 hours, with wide inter individual variability. The plasma concentration of Granisetron is not clearly correlated with antiemetic efficacy. The therapeutic effect can still be present even when Granisetron is no longer detectable in plasma. The pharmacokinetics of intravenously administered Granisetron is essentially linear at intravenous doses up to 4 times the recommended clinical dose.
Pharmacokinetics in special patient populations
In elderly patients, pharmacokinetic parameters after single intravenous doses were within the range found in young patients.
In patients with severe renal failure, pharmacokinetic parameters after single intravenous doses were generally similar to those in normal patients.

In patients with hepatic impairment due to neoplastic changes, total plasma clearance of an intravenous dose was approximately half that of patients with normal liver function. Despite these changes, no dosage adjustment is necessary. Kinetics in children: When Granisetron is administered at a dose of 20 μg/kg body weight, its pharmacokinetics do not differ to any clinically significant extent in adults as compared to children.

5.3. Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproductive toxicity and genotoxicity.

Carcinogenicity studies revealed no special hazard for humans when used in the recommended human dose. However, when administered in higher doses and over a prolonged period of time the risk of carcinogenicity cannot be ruled out.

A study in cloned human cardiac ion channels has shown that Granisetron has the potential to affect cardiac repolarization via blockade of HERG potassium channels. Granisetron has been shown to block both sodium and potassium channels, which potentially affects both depolarization and repolarization through prolongation of PR, QRS, and QT intervals. This data helps to clarify the molecular mechanisms by which some of the ECG changes (particularly QT and QRS prolongation) associated with this class of agents occur. However, there is no modification of the cardiac frequency, blood pressure or the ECG trace. If changes do occur, they are generally without clinical significance

6. Pharmaceutical particulars

6.1. List of excipients

Sodium chloride,Citric acid monohydrate, Sodium hydroxide, Sodium citrate & Water for injections.

6.2. Incompatibilities

NA

6.3. Shelf life

2 years

6.4. Special precautions for storage

Do not store above 30°C, do not freeze and Keep container in outer carton, in order to protect from light.

6.5 Nature and contents of container

Glass vial 3ml type 1 with Rubber stopper 13 mm

6.6 Special precautions for disposal and other handling

SETONIX® is chemically and physically stable for at least 24 hours at room temperature (15-25 ℃) in normal indoor illumination (daylight plus florescent light) in the following solutions: 0.9% NaCl and 5% Dextrose. Infusion preparation:

Ideally, SETONIX® Infusions should be prepared shortly before use

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder

MS Pharma – Jordan
King Abdullah (II) Bin Al-Hussein Industrial Estate, Amman Jordan
Telephone +962 6 40 20 680
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Manufacturing site address

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8. Marketing Authorization Number

CTD7995

9. Date of first <registration> / renewal of the <registration>

23/02/2024

10. Date of revision of the text

Novemeber,2024