

**Nasea adalah obat baru yang terdaftar tahun 2003.
Informasi di bawah ini merupakan informasi update tahun 2010.**

Antiemetic 5-HT₃ receptor antagonist

**Nasea® Injection 0.3 mg
<Ramosetron hydrochloride>
Powerful drug, Designated drug, and Prescription-only drug**

DESCRIPTION

Brand name	Nasea® Injection 0.3 mg
Ingredient/content (Content per ampule)	Ramosetron hydrochloride 0.15 mg/mL
pH	4.0-5.0
Osmotic pressure ratio (to physiological saline)	Approximately 1
Description	Clear, colorless solution for injection in brown ampule

INDICATIONS

- Therapy for Gastrointestinal symptoms (nausea and vomiting) associated with carcinostatics (such as cisplatin)
- Management of post-operative nausea and vomiting

DOSAGE AND ADMINISTRATION

The recommended intravenous adult dosage is 0.3 mg of ramosetron hydrochloride once a day. Dosage may be adjusted depending on the patient's age and symptoms. If a sufficient response is not achieved, an additional 0.3 mg dose may be given. However, the maximum dosage is 0.6 mg a day.

PRECAUTIONS

1. Important Precautions

If this product is used for gastrointestinal symptoms (nausea and vomiting) associated with carcinostatics (such as cisplatin), it should only be used to treat severe nausea and vomiting.

2. Adverse Reactions

Adverse reactions (including abnormalities in clinical laboratory findings) with this product were observed in 18 (5.1%) of 352 patients investigated in the clinical trials until approval, and 236 (7.2%) of 3,299 patients treated in the drug-use results surveys and the post-marketing clinical trials (at the time application for drug reexamination in Japan).

The adverse reactions described below were reported in the above trials and/or surveillance, spontaneous reports, or others.

(1) Clinically significant adverse reactions

Shock and anaphylactoid symptoms (incidence unknown): Shock or anaphylactoid symptoms (such as ill feeling, feeling of chest distress, dyspnea, wheezing, hot facial flashes, redness, itching, cyanosis, and hypotension, etc) may occur. Patients therefore should be carefully observed, and if such reaction develop during treatment with Nasea® Injection 0,3 mg, discontinue treatment and institute appropriate medical therapy.

(2) Clinically significant adverse reactions (analog)

Epileptiform attacks: Epileptiform attacks have been reported with other 5-HT₃ receptor antagonist antiemetics in foreign countries.

(3) Other adverse reactions

	5% > ≥ 1%	1% > ≥ 0,1%	0.1% >	Incidence unknown
Hypersensitivity (Note)		Rash	Itching	Redness
Nervous System / psychiatric		Headache	Headache dull	
Gastrointestinal		Diarrhea	Constipation	
Kidney		BUN increased, blood creatinine increased		
Hepatic	Hepatic dysfunction (AST (GOT) increased, ALT (GPT) increased, gamma-GTP increased, bilirubin increased, etc)			
Others		Hot feeling generalized, hiccup	Head hot-flushes, numbness of tongue	

Note) If such a reaction develops, discontinue treatment.

3. Geriatric Use

It is advisable to cautiously administer the drug under careful observation of the patients condition. If any adverse reaction develops, appropriate measures such as drug discontinuation should be taken. [The elderly are more likely to have a physiological hypofunction].

4. Pregnancy and Nursing Mothers

- (1) This product should be used during pregnant women or women who may possibly be pregnant only if the expected therapeutic benefit outweigh the possible risks associated with treatment. [The safety of this product in pregnant women has not been established].
- (2) Nursing mothers should discontinue breast feeding during treatment. [It has been reported that ramosetron hydrochloride is excreted in the milk of lactating rats.]

5. Pediatric Use

Safety in neonates, newborns, sucklings, infants, and children has not been established [insufficient clinical experience].

6. Precautions concerning Use

- (1) Caution in preparation:
As Nasea[®] Injection 0.3 mg has been demonstrated to be incompatible with the following injections, the drug should not be combined with any of these injectable solutions:

D-mannitol injection, Lunetoron[®] Injection and Lasix[®] Injection.

However, the product is compatible with Lasix[®] Injection if one ampule of this product is combined with Lasix[®] Injection containing 20 mg of furosemide in 200 mL of physiological saline.
- (2) At ampule cutting:
The ampule of Nasea[®] Injection 0.3 mg is a one-point-cut type. It is recommended that the cut point of ampule be wiped clean with an ethanol swab before cutting.

PHARMACOKINETICS

<Absorption, metabolism and excretion>

Intravenous injection of ramosetron hydrochloride into healthy subjects at doses of 0.1 to 0.8 mg showed that the plasma concentration of the unchanged drug declined biphasically with a $t_{1/2\beta}$ of approximately 5 h. The AUC was directly proportional to the dose. Nasea[®] Injection 0.3 mg showed linear pharmacokinetics. During the first 24 hours after injection, 16% to 22% of the dose was excreted as unchanged drug in urine.

In addition to the unchanged drug, both the demethylated and hydroxylated metabolites and their conjugates were detected in urine. In healthy volunteers receiving repeated doses, the pharmacokinetic profile remained unaltered and there was no evidence of accumulation.

The results of the in vitro metabolism study show that the hepatic drug metabolizing enzymes

CYP1A1, CYP1A2, and CYP2D6 are involved in the primary metabolism of ramosetron hydrochloride in humans.

<Pharmacokinetic parameters in healthy adult volunteers after Intravenous doses>

Dosage	t _{1/2β} (hr)	AUC _{0-α} (ng.hr/mL)	CL total (L/hr/kg)	Vdss (L/kg)
0.2 mg	4.33	9.86	0.30	1.69
0.4 mg	5.78	24.95	0.27	2.11
0.8 mg	5.44	41.64	0.29	2.07

<Pharmacokinetic parameters in healthy adult volunteers and tumor patients>

	C _{15 min} (ng/mL)	t _{1/2β} (hr)	AUC _{0-4hr} (ng.hr/mL)	Plasma protein binding rate (%)
Healthy adult volunteers	2.42	5.78	6.57	91.2
Tumor patients	4.97	9.02	12.49	85.9

(At administered ramosetron hydrochloride 3 mg)

CLINICAL STUDIES

Double-blind controlled clinical trials and open clinical studies were conducted at a total of 121 medical institutions. A total of 357 patients with nausea and vomiting associated with antineoplastics (such as cisplatin) were enrolled. Summaries of these clinical studies are provided below.

The usefulness of Nasea[®] Injection 0.3 mg has been demonstrated by double-blind placebo controlled clinical trials in patients with nausea and vomiting caused by antineoplastics (such as cisplatin).

Dosage	Efficacy rate for control of nausea and vomiting following carcinostatics such as cisplatin	Efficacy rate for prevention of nausea and vomiting by administration prior to carcinostatics such as cisplatin
0.3 mg	79.8% (178 cases out of 223)	85.1% (40 cases out of 47)

PHARMACOLOGY

<Pharmacokinetics>

1. 5-HT₃ receptor antagonistic effect

Ramosetron hydrochloride showed 5-HT₃ receptor antagonistic effects on serotonin-induced contraction of isolated guinea pig colon and bradycardic reflexes (Bezold-Jarisch reflex) in rats and ferrets.

2. Efficacy of antiemetic vomiting induced by a carcinostatic

Vomiting induced by injection of cisplatin was prevented or arrested in ferrets by administration of ramosetron hydrochloride prior to onset of vomiting or after initial development of vomiting.

<Mechanism of action>

Carcinostatics such as cisplatin cause enterochromaffin cells in the gastrointestinal tract to release serotonin. This released serotonin binds to 5-HT₃ receptors present in the afferent vagal nerve-endings in the gastrointestinal mucosa, and this neurostimulation induces emesis via the vomiting center. Ramosetron hydrochloride is thought to exert its antiemetic action by blocking 5-HT₃ receptors.

PHYSICOCHEMISTRY

Nonproprietary name:

Ramosetron hydrochloride

Chemical name :

(-)-(R)-5-[(1-methyl-1*H*-indol-3-yl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole monohydrochloride

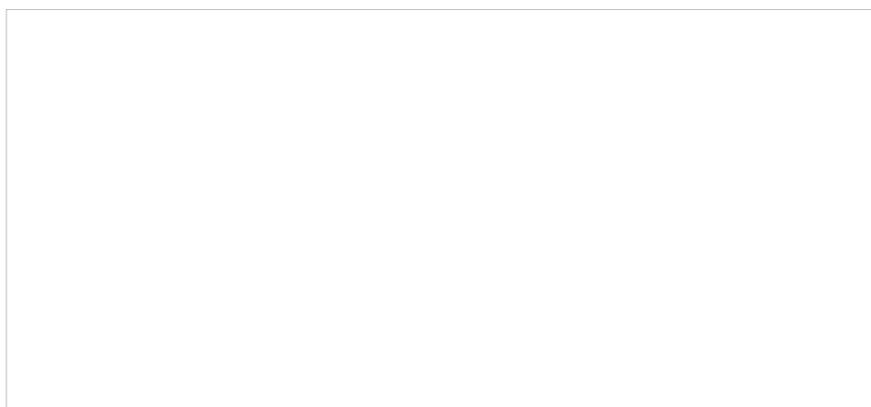
Molecular formula :

C₁₇H₁₇N₃O.HCl

Molecular weight:

315.80

Structural formula :



Description :

Ramosetron hydrochloride occurs as a white to pale yellowish white crystalline powder. It is freely soluble in water and in methanol, soluble in ethanol and in glacial acetic acid, very slightly soluble in acetonitrile and in acetic anhydride, and practically insoluble in tetrahydrofuran and in ether. Ramosetron hydrochloride is hygroscopic and sensitive to light.

PACKAGING

Nasea® Injection 0.3 mg (2 mL/ampule):

Box @ 5 ampules

Store below 25⁰C, protect from light.

Approved Shelf life : 36 months

“Harus dengan resep dokter”

No. Reg. : DKL1004131743A1

Manufactured by **Astellas Tokai Co.Ltd**, for

Astellas Pharma Inc., Japan

Imported by **PT. Combiphar, Indonesia**

Repacked by **PT. Combiphar, Bandung, Indonesia**