For use in India only
To be sold by retail only under the prescription of Gastroenterologist or Hepatologist only.

PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS
See full prescribing information for complete boxed warning.

- **Plecanatide is contraindicated in patients less than 6 years of age. Plecanatide caused death due to dehydration.**
- **Avoid use of Plecanatide in patients 6 years to less than 18 years of age.**
- **The safety and effectiveness of Plecanatide have not been established in patients less than 18 years of age.**

1. GENERIC NAME

Plecanatide Tablets 3 mg

Plectide प्लेक्टाइड

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Plecanatide Tablets 3 mg
Each uncoated tablet Contains
Plecanatide….3 mg

3. DOSAGE FORM AND STRENGTH

Plecanatide is available as 3 mg tablets.

4. CLINICAL PARTICULARS

4.1. Indications

Plecanatide is indicated in adults for the treatment of Chronic idiopathic constipation (CIC) and Irritable bowel syndrome with constipation (IBS-C).

4.2. Posology and Method of Administration

The recommended dosage of Plecanatide for the treatment of CIC and IBS-C is 3 mg taken orally once daily.

Preparation and Administration Instructions

- Plecanatide can be taken with or without food.
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take two doses at the same time.
- Swallow a tablet whole for each dose.
- For adult patients with swallowing difficulties, Plecanatide tablets can be crushed and administered orally either in applesauce or with water or administered with water via a nasogastric or gastric feeding tube. Mixing Plecanatide crushed tablets in other soft foods or in other liquids has not been tested.

Oral Administration in Applesauce:

1. In a clean container, crush the Plecanatide tablet to a powder and mix with 1 teaspoonful of room temperature applesauce.
2. Consume the entire tablet-applesauce mixture immediately. Do not store the mixture for later use.

Oral Administration in Water:

1. Place the Plecanatide tablet in a clean cup.
2. Pour approximately 30 mL of room temperature water into the cup.
3. Mix by gently swirling the tablet and water mixture for at least 10 seconds. The Plecanatide tablet will fall apart in the water.
4. Swallow the entire contents of the tablet water mixture immediately.
5. If any portion of the tablet is left in the cup, add another 30 mL of water to the cup, swirl for at least 10 seconds, and swallow immediately.
6. Do not store the tablet-water mixture for later use.

Administration with Water via a Nasogastric or Gastric Feeding Tube:

1. Place the Plecanatide tablet in a clean cup with 30 mL of room temperature water.
2. Mix by gently swirling the tablet and water mixture for at least 15 seconds. The Plecanatide tablet will fall apart in the water.
3. Flush the nasogastric or gastric feeding tube with 30 mL of water using a catheter tip syringe.
4. Draw up the mixture using the syringe and immediately administer via the nasogastric or gastric feeding tube. Do not reserve for future use.
5. If any portion of the tablet is left in the cup, add another 30 mL of water to the cup, swirl for at least 15 seconds, and using the same syringe, administer via the nasogastric or gastric feeding tube.
6. Using the same or a fresh syringe, flush the nasogastric or gastric feeding tube with at least 10 mL of water.

4.3. Contraindications

Plecanatide is contraindicated in

- Patients less than 6 years of age due to the risk of serious dehydration
- Patients with known or suspected mechanical gastrointestinal obstruction.

4.4. Special Warnings and Precautions for Use

Risk of Serious Dehydration in Pediatric Patients

Plecanatide is contraindicated in patients less than 6 years of age. The safety and effectiveness of Plecanatide in patients less than 18 years of age have not been established Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years of age and older to develop severe diarrhea and its potentially serious consequences.
Avoid the use of Plecanatide in patients 6 years to less than 18 years of age.

Diarrhea

If severe diarrhea occurs, suspend dosing and rehydrate the patient.

4.5. Drug Interactions

Neither plecanatide nor its active metabolite inhibited the cytochrome P450 (CYP) enzymes 2C9 and 3A4, and they did not induce CYP3A4 *in vitro*. Plecanatide and its active metabolite were neither substrates nor inhibitors of the transporters Pglycoprotein (P-gp) or breast cancer resistance protein (BCRP) *in vitro*.

4.6. Use in Special Populations (such as pregnant women, **lactating women, paediatric patients, geriatric patients etc.)**

Pregnancy

Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration and maternal use is not expected to result in fetal exposure to the drug. The available data on Plecanatide use in pregnant women are not sufficient to inform any drug associated risks for major birth defects and miscarriage. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Lactation

There is no information regarding the presence of plecanatide in human milk, or its effects on milk production or the breastfed infant. Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration.
It is unknown whether the negligible systemic absorption of plecanatide by adults will result in a clinically relevant exposure to breastfed infants. Exposure to plecanatide in breastfed infants has the potential for serious adverse effects. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Plecanatide and any potential adverse effects on the breastfed infant from Plecanatide or from the underlying maternal condition.

Pediatric Use

Plecanatide is contraindicated in pediatric patients less than 6 years of age. Avoid use of Plecanatide in patients 6 years to less than 18 years of age. The safety and effectiveness of Plecanatide in patients less than 18 years of age have not been established. Because of increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years of age and older to develop diarrhea and its potentially serious consequences. Plecanatide is contraindicated in patients less than 6 years of age.

Geriatric Use

The safety and effectiveness of Plecanatide in patients greater than 65 years of age have not been established.

4.7. Effects on Ability to Drive and Use Machines

Plecanatide has no or negligible influence on the ability to drive and use machines. During treatment with Plecanatide, dizziness has been reported as less common adverse reaction. Therefore, patients who experience dizziness should be cautious while driving or using machines.

4.8. Undesirable Effects

Tabulated list of adverse reactions

System organ class	Most Common	Common	Less Common	Rare
Infections and infestations			Sinusitis; Nasopharyngitis; Upper respiratory tract infection; Urinary tract infection	
Nervous system disorders			Dizziness	
Gastrointestinal disorders	Diarrhoea		Nausea; Abdominal distension; Flatulence; Abdominal tenderness	
Hepatobiliary disorders			Increased liver biochemical tests	

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

There is no specific treatment to the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Plecanatide is a structural analog of human uroguanylin, and similarly to uroguanylin, plecanatide functions as a guanylate cyclase-C (GC-C) agonist. Both plecanatide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation of extracellular cGMP has been associated with a decrease in the activity of painsensing nerves in animal models of visceral pain. Elevation of intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit.

5.2 Pharmacodynamic Properties

Food Effect

Subjects who received either a low-fat, low calorie (LF-LC) meal or a high fat, high calorie (HF-HC) meal reported looser stools than fasted subjects up to 24 hours after a single dose of plecanatide 9 mg (3 times the recommended dose). In clinical studies, plecanatide was administered with or without food.

5.2 Pharmacokinetic Properties

Absorption

Plecanatide was minimally absorbed with negligible systemic availability following oral administration. Concentrations of plecanatide and its active metabolite in plasma were below the limit of quantitation in the majority of analyzed plasma samples after an oral plecanatide dose of 3 mg. Therefore, standard pharmacokinetic parameters such as AUC, C_{max}, and half-life ($t_{1/2}$) could not be calculated.

Distribution

Given that plecanatide concentrations following clinically relevant oral doses were not measurable, plecanatide is expected to be minimally distributed in tissues. Oral plecanatide was localized to the GI tract where it exerted its effects as a GC-C agonist with negligible systemic exposure. Plecanatide exhibited little to no binding to human serum albumin or human α-1-acid glycoprotein.

Elimination

Metabolism

Plecanatide was metabolized in the GI tract to an active metabolite by loss of the terminal leucine moiety. Both plecanatide and the metabolite were proteolytically degraded within the intestinal lumen to smaller peptides and naturally occurring amino acids.

Excretion

Plecanatide and its active metabolite were not measurable in plasma following administration of the recommended clinical doses.

Drug-Drug Interactions

Neither plecanatide nor its active metabolite inhibited the cytochrome P450 (CYP) enzymes 2C9 and 3A4, and they did not induce CYP3A4 *in vitro*.
Plecanatide and its active metabolite were neither substrates nor inhibitors of the transporters P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) *in vitro*.

6. NONCLINICAL PROPERTIES

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of plecanatide was assessed in 2-year carcinogenicity studies in mice and rats. Plecanatide was not tumorigenic in mice at oral doses up to 90 mg/kg/day or in rats at oral doses up to 100 mg/kg/day. Limited systemic exposure to plecanatide was achieved at the tested dose levels in animals, whereas no detectable exposure occurred in humans. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.
Plecanatide was not genotoxic in the *in vitro* bacterial reverse mutation (Ames) assay, *in vitro* mouse lymphoma mutation assay, or the *in vivo* mouse bone marrow micronucleus assay.
Plecanatide had no effect on fertility or reproductive function in male or female mice at oral doses of up to 600 mg/kg/day.

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities

None

7.2 Packing Information

10's Blister pack and 30's bottle pack.

7.3 Storage and Handling Instructions

Store at temperature below 25°C.

8. PATIENT COUNSELING INFORMATION

Advise patients:

Diarrhea

To stop Plecanatide and contact their healthcare provider if they experience severe diarrhea.

Accidental Ingestion

Accidental ingestion of Plecanatide in children, especially in children less than 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to take steps to store Plecanatide securely and out of reach of children and to dispose of unused Plecanatide.

Administration and Handling Instructions

- To take Plecanatide once daily with or without food
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take two doses at the same time.
- To swallow Plecanatide tablets whole.
- If adult patients have swallowing difficulties, Plecanatide tablets can be crushed and administered orally in either applesauce or with water, or administered with water via a nasogastric or gastric feeding tube.
- To keep Plecanatide in a dry place. Protect from moisture. For bottles, keep Plecanatide in the original bottle. Do not remove desiccant from the bottle. Do not subdivide or repackage. Remove and discard polyester coil after opening. Keep bottles closed tightly.

9. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited,
Formulation Division, Unit II,
Sy.no.1277, 1319 to 1324,
Nandigama (Village & Mandal),
Ranga Reddy District
Telangana-509228,
India.

10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

5/MN/TS/2014/F/G, 26/08/2019

11. DATE OF REVISION

June-2023

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