Front

Prutide

(P r u c a l o p r i d e)

Tablet

پـروٹائیڈ

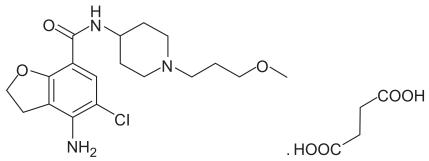
COMPOSITION:
PrutideTablet 1 mg:
Each film coated tablet contains:
Prucalopride as Succinate ..... 1 mg.

Product Specs.: Innovator

PrutideTablet 2 mg:
Each film coated tablet contains:
Prucalopride as Succinate ..... 2 mg.

Product Specs.: Innovator

DESCRIPTION:
Prucalopride tablets for oral use contain prucalopride succinate, a dihydrobenzofurancarboxamide that is a serotonin type 4 (5-HT4) receptor agonist. The IUPAC name is: 4-amino-5-chloro-N-[1-(3-methoxypropyl)piperidin-4-yl]-2,3-dihydrobenzofuran-7-carboxamide succinate. The molecular formula is $C_{18}H_{26}ClN_3O_3.C_4H_6O_4$ and the molecular weight is 485.96. The structural formula is:



Prucalopride succinate is a white to almost white powder. It is highly soluble in acidic aqueous media and alkaline aqueous media up to a pH of approximately 9.

CLINICAL PHARMACOLOGY:
Mechanism of Action:
Prucalopride, a selective serotonin type 4 (5-HT4) receptor agonist, is a gastrointestinal (GI) prokinetic agent that stimulates colonic peristalsis (high-amplitude propagating contractions [HAPCs]), which increases bowel motility. Prucalopride was devoid of effects mediated via 5-HT2A, 5-HT2B, 5-HT3, motilin or CCK-A receptors in vitro at concentrations exceeding 5-HT4 receptor affinity by 150-fold or greater. In isolated GI tissues from various animal species, prucalopride facilitated acetylcholine release to enhance the amplitude of contractions and stimulate peristalsis. In rats and dogs, prucalopride stimulated gastrointestinal motility with contractions starting from the proximal colon to the anal sphincter.
Pharmacodynamics:
High Amplitude Propagating Contractions Following a single 2-mg dose of prucalopride in patients with CIC, prucalopride increased the number of high amplitude propagating contractions (HAPCs) during the first 12 hours as compared with an osmotic laxative treatment. In addition, prucalopride 4 mg once daily (2 times the maximum human recommended dose of 2 mg) for 7 days increased the amplitude of HAPCs in healthy subjects without affecting colonic phasic activity as compared with placebo.

Pharmacokinetics: The pharmacokinetics of prucalopride has been evaluated in healthy subjects and is dose-proportional within and beyond the therapeutic range (tested up to 20 mg, 10 times the maximum approved recommended dose). Prucalopride administered once daily displays time-independent kinetics during prolonged treatment. With once daily administration of 2 mg prucalopride, pharmacokinetic steady-state is attained within 3 to 4 days, and steady-state plasma concentrations fluctuate between trough and peak values of 2.5 and 7 ng/mL, respectively, with mean plasma AUC0-24h of 109 ng•h/mL. The accumulation ratio after once daily dosing ranged from 1.9 to 2.3. The terminal half-life is approximately 1 day. Pharmacokinetic parameters in patients with CIC are similar to those seen in healthy subjects.
Absorption: Following a single oral dose of 2 mg prucalopride in healthy subjects, peak plasma concentrations are observed within 2 to 3 hours after administration. The absolute oral bioavailability is >90%. Effect of Food Concomitant intake with a high-fat meal (1000 kcal total, 500 kcal from fat) does not influence the oral bioavailability of prucalopride
Distribution: Prucalopride has a steady-state volume of distribution (Vss) of 567 liters after intravenous administration. The plasma protein binding of prucalopride is approximately 30%.
Elimination: Renal excretion is the main route of elimination of prucalopride. Non-renal elimination contributes up to about 35% of the total. The plasma clearance of prucalopride averages 317 mL/min.
Metabolism: Prucalopride is a substrate of CYP3A4, in vitro. In an oral dose study with radiolabeled prucalopride in healthy subjects, prucalopride made up 92 to 94% of the total radioactivity in plasma. There are 7 different known minor metabolites, the most abundant metabolite (O-desmethyl prucalopride acid) represents 0 to 1.7% of the total plasma exposure.
Excretion: Following oral administration of radiolabeled prucalopride in healthy subjects, 60 to 65% of the administered dose is excreted unchanged in urine and about 5% in feces. On average, 84.2% of administered radioactive dose was recovered in urine and 13.3% of the dose was recovered in feces. Seven metabolites were recovered in urine and feces, with the most abundant metabolite (Odesmethyl prucalopride acid) accounting for 3.2% and 3.1% of the dose in urine and feces, respectively. None of the other metabolites accounted for more than 3% of the dose. Renal elimination of prucalopride involves both passive filtration and active secretion.

INDICATIONS AND USAGE:
Prucalopride is indicated for the treatment of chronic idiopathic constipation (CIC) in adults.

DOSAGE AND ADMINISTRATION:
Prucalopride can be taken with or without food. The recommended dosage by patient population is:

Table 1: Recommended Dosage Regimen and Dosage Adjustments by Population

Population with CIC	Recommended Oral Dose Regimen
Adults	2 mg once daily
Patients with severe renal impairment (creatinine clearance (CrCL) less than 30 mL/min)	1 mg once daily

Back

CONTRAINDICATIONS:

Prucalopride is contraindicated in patients with:

- A history of hypersensitivity to Prucalopride. Reactions including dyspnea, rash, pruritus, urticaria, and facial edema have been observed
- Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum.

WARNINGS AND PRECAUTIONS:

Suicidal ideation and behaviour:

In clinical trials, suicides, suicide attempts, and suicidal ideation have been reported. A causal association between treatment with Prucalopride and an increased risk of suicidal ideation and behaviour has not been established. Monitor all patients treated with Prucalopride for persistent worsening of depression or the emergence of suicidal thoughts and behaviours. Counsel patients, their caregivers, and family members of patients to be aware of any unusual changes in mood or behaviour and alert the healthcare provider. Instruct patients to discontinue Prucalopride immediately and contact their healthcare provider if they experience any of these symptoms.

ADVERSE REACTIONS:

Most common adverse reactions (⩾ 2%) are headache, abdominal pain, nausea, diarrhea, abdominal distension, dizziness, vomiting, flatulence, and fatigue.

Less common adverse reactions occurring in <2% of patients receiving Prucalopride 2 mg once daily include: Gastrointestinal disorders: abnormal gastrointestinal sounds Metabolism and nutrition disorders: decreased appetite Nervous system disorders: migraine Renal and urinary disorders: pollakiuria

Diarrhea:

Of the patients who reported diarrhea, 70% (110 out of 157) reported it in the first week of treatment. Diarrhea typically resolved within a few days in 73% (80 out of 110) of those patients. Severe diarrhea was reported in 1.8% of patients treated with Prucalopride 2 mg compared to 1% of patients in the placebo group, and had a similar onset and duration as diarrhea overall.

Headache:

Of the patients who reported headache, 66% (157 out of 237) treated with Prucalopride 2 mg once daily reported onset in the first 2 days of treatment. Symptoms typically resolved within a few days in 65% (102 out of 157) of those patients.

Adverse reactions leading to discontinuation:

In the 6 clinical trials described above, 5% of patients treated with 2 mg of Prucalopride once daily discontinued due to adverse reactions, compared to 3% of patients in the placebo group. The most common adverse reactions leading to discontinuation were nausea (2% Prucalopride, 1% placebo), headache (1% Prucalopride, 1% placebo), diarrhea (1% Prucalopride),

USE IN SPECIFIC POPULATIONS:

Pregnancy:

Available data from case reports with Prucalopride use in pregnant women are insufficient to identify any drug-associated risks of miscarriage, major birth defects, or adverse maternal or fetal outcomes.

Lactation:

Prucalopride is present in breast milk. There are no data on the effects of Prucalopride on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Prucalopride and any potential adverse effects on the breastfed child from Prucalopride or from the underlying maternal condition.

Paediatric use:

The safety and effectiveness of Prucalopride have not been established in pediatric patients.

Geriatric use:

Elderly subjects had higher Prucalopride exposure compared to younger subjects. However, the effect of age on the pharmacokinetics of Prucalopride appeared to be related to decreased renal function Adjust the dosage in elderly patients based on renal function

Renal impairment:

No dosage adjustment is required for patients with mild and moderate renal impairment (creatinine clearance at least 30 mL/min, as determined from a 24-hour urine collection in the clinical trial).

Prucalopride is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. A decreased dosage is recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min, as determined from a 24-hour urine collection in the clinical trial)

OVERDOSAGE:

An overdose may result in appearance of symptoms from an exaggeration of the known pharmacodynamic effects of Prucalopride and includes headache, nausea, and diarrhea. Specific treatment is not available for Prucalopride overdose. Should an overdose occur, treat symptomatically and institute supportive measures, as required. Extensive fluid loss from diarrhea or vomiting may require correction of electrolyte disturbances.

INSTRUCTIONS:

- Store below 30°C.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Prutide Tablet 1 mg	:	Pack of 1 x 10 tablets.
Prutide Tablet 2 mg	:	Pack of 1 x 10 tablets.

ہدایات:

۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

گرمی، دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
Weather Folds Pharmaceuticals
Plot No. 69/2, Phase-II, Industrial Estate, Hattar, Pakistan.

FOR FURTHER INFORMATION PLEASE CONTACT:

Marketed by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.