Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

REFLAD 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg of itopride hydrochloride.

Excipient with known effect

Each film-coated tablet contains 70.95 mg of lactose (as lactose monohydrate).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White to almost white round biconvex film-coated tablets with score line, diameter 7 mm.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of gastrointestinal symptoms of functional dyspepsia caused by reduced gastrointestinal motility.

The medicinal product is intended for adults.

4.2 Posology and method of administration

Posology
The recommended dose for adults is 1 tablet 3 times a day before meal, corresponding to 150 mg of itopride daily. The maximum daily dose is 150 mg of itopride.
This dose can be reduced if required in the course of disease. The exact dosage and duration of treatment depends on the clinical state of the patient. REFLAD should not be used for more than 8 weeks (see section 5.1).

Paediatric population
Safety of this product in children under the age of 16 has not been established.

Hepatic or renal impairment
Itopride is metabolised in liver. Itopride and its metabolites are excreted mainly via kidneys (see section 5.2). Patients with reduced hepatic or renal functions should be carefully monitored and in case of adverse reactions it is necessary to take appropriate measures, as e.g. to reduce the dosage or to discontinue the therapy.

Elderly
It was shown in clinical studies that the incidence of adverse effects in patients aged 65 years and older was not higher than in younger patients. Itopride should be administered in elderly patients with adequate caution because of increased incidence of hepatic and renal function disorders, other diseases or treatment with additional drugs.

Method of administration
Tablets should be swallowed whole with a sufficient amount of liquid, before meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

REFLAD should not be used in patients in whom increased gastrointestinal motility could be harmful, e.g. in patients with gastrointestinal haemorrhage, mechanical obstruction or perforation.

4.4 Special warnings and precautions for use

Itopride potentiates acetylcholine action and can induce cholinergic side effects.
Data about long-term administration of itopride is not available.

Hepatic or renal impairment
Itopride is metabolised in liver. Itopride and its metabolites are excreted mainly via kidneys. Patients with reduced hepatic or renal functions should be carefully monitored and in case of adverse reactions it is necessary to take appropriate measures, as e.g. to reduce the dosage or to discontinue the therapy.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per one tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction was detected when itopride was administered concomitantly with warfarin, diazepam, diclofenac, ticlopidine, nifedipine and nicardipine.
Drug-drug interactions that arise due to cytochrome P450 metabolism are not assumed because itopride is metabolised mainly by flavine monooxygenase.
Itopride has gastrokinetic effect that could influence the absorption of concomitantly orally administered medicines. Particular attention should be paid to medicines with a narrow therapeutic index, medicines with prolonged-release of the active substance and enteric-coated drug formulations.
Anticholinergic agents may reduce the action of itopride.
Substances as cimetidine, ranitidine, teprenone and cetrexate do not affect prokinetic activity of itopride.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of itopride in pregnant women. Therefore itopride can be used during pregnancy and in women of childbearing potential only if therapeutic benefits outweigh possible risks considerably.

Breast-feeding
Itopride is excreted in the milk of lactating rats. Due to the potential for adverse reactions in infants, a decision must be made whether to discontinue breast-feeding or to abstain from itopride therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No effects of itopride on fertility have been shown (see section 5.3).

4.7 Effects on ability to drive and use machines

Although no effects on ability to drive and use machines have been found, impairment of alertness cannot be ruled out since dizziness may occur very rarely.

4.8 Undesirable effects

Adverse reactions have been ranked according to MedDRA terminology under headings of frequency using the following convention:
very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Itopride was well tolerated and no serious adverse reactions were observed during clinical trials.

System Organ Class	Side effect	Frequency
Blood and lymphatic system disorders	Leucopenia*	Uncommon
	Thrombocytopenia	Not known
Immune system disorders	Anaphylactoid reaction	Not known
Endocrine disorders	Hyperprolactinaemia**	Uncommon
	Gynecomastia	Not known
Nervous system disorders	Headache	Uncommon
	Dizziness	Uncommon
	Tremor	Not known
Gastrointestinal disorders	Diarrhoea	Uncommon
	Constipation	Uncommon
	Abdominal pain	Uncommon
	Hypersalivation	Uncommon
	Nausea	Not known
Hepatobiliary disorders	Jaundice	Not known
Skin and subcutaneous tissue disorders	Rash	Rare
	Erythema	Rare
	Pruritus	Rare
Investigations	AST increased	Not known
	ALT increased	Not known
	Gamma-GTP increased	Not known
	Alkaline phosphatase increased	Not known
	Bilirubin increased	Not known

* Careful observation should be made through haematological examination. The treatment should be discontinued when any abnormality is observed.
**If galactorrhea or gynecomastia occur, the treatment must be interrupted or terminated.

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. Healthcare professionals are asked to report any suspected adverse reactions via
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Overdose was not experienced in humans. In case of overdose the usual measures of gastric lavage and symptomatic therapy should be applied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Drugs for functional gastrointestinal disorders, propulsives; ATC code: A03FA07

Mechanism of action
Itopride activates the gastrointestinal propulsive motility by dopamine D_2 receptors antagonistic action and acetylcholine esterase inhibitory action. Itopride activates acetylcholine release and inhibits its degradation. In addition, itopride has an antiemetic action which is based on interaction with dopamine D_2 receptors in chemoreceptor zone. This action was demonstrated by dose dependent inhibition of apomorphine induced vomiting in dogs.
Itopride accelerates stomach emptying in humans and does not influence plasma concentrations of gastrin.
Itopride has high specific action in upper part of gastrointestinal tract, where it positively effects functional dyspepsia, defined by one or more symptoms: postprandial fullness, early satiety, epigastric pain, and epigastric burning and no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.
The duration of the administration in clinical studies was maximally 8 weeks.

5.2 Pharmacokinetic properties

Absorption
Itopride is absorbed rapidly and almost completely from gastrointestinal tract. Relative bioavailability about 60% is due to first-pass effect. Food does not affect bioavailability of the product. Maximum plasma concentrations are reached in 30 to 45 minutes after administration of 50 mg of itopride.
After repeated administration of doses in the range of 50 to 200 mg 3 times a day for period of 7 days, itopride and its metabolites have shown pharmacokinetics of linear type with minimal accumulation.

Distribution
About 96% of itopride is bound on plasma proteins, mainly albumin. Less than 15% of itopride bound part is bound on alpha-1-acid-glycoprotein.
In rats itopride is distributed extensively in the tissues (Vd_{β} = 6.1 l/kg) except for central nervous system; high concentrations are reached in kidneys, small intestine, liver, adrenal glands and stomach. Protein binding in rats was lower than in humans (78% contrary to 96%). Penetration into the central nervous system was minimal. Itopride is excreted in milk of lactating rats.

Biotransformation
Itopride is extensively metabolised in liver in humans. Three metabolites were identified of which only one manifests minor activity without pharmacological significance (about 2 to 3% of itopride effect).
Itopride is metabolised by flavine monoxygenase (FMO3). The amount and efficacy of human FMO isoenzymes can be associated with genetic polymorphism which can result in rare autosomal recessive condition known as trimethylaminuria (fish odour syndrome). Biological half-life in patients with trimethylaminuria can be longer.
Pharmacokinetic *in vivo* studies of CYP-mediated reactions did not prove inhibition or induction CYP2C19 and CYP2E1 caused by itopride. Administration of itopride did not influence content of CYP or the activity of uridine-diphosphate-glucuronyl transferase.

Elimination
Itopride and its metabolites are primarily excreted by urine. The amount of excreted itopride and N-oxide after oral single therapeutic dose to healthy volunteers was 3.7% and 75.4% respectively.
Half-life of itopride is about 6 hours.

5.3 Preclinical safety data

Preclinical safety studies were carried out only at exposures considered sufficiently in excess of therapeutic human doses indicating little relevance to clinical use. In addition humans are less sensitive to hormonal effects observed in animals.
High doses of itopride (30 mg/kg/day) caused hyperprolactinaemia and secondary reversible hyperplasia of uterine mucosa in rats, but not in dogs (dose up to 100 mg/kg/day) or primates (dose up to 300 mg/kg/day).
In a 3-month toxicity study in dogs, prostate atrophy was observed after oral doses of 30 mg/kg/day, but not after 6-month oral administration of higher doses (100 mg/kg/day) in rats, nor more higher doses (300 mg/kg/day) in primates.
Long-term studies of carcinogenic potential in animals have not been carried out.
No clastogenic or mutagenic effects of itopride were found in a series of *in vitro* and *in vivo* tests.
Fertility studies in female rats receiving doses of 30 mg/kg/day and higher, showed hyperprolactinaemia and secondary prolongation of oestral cycle. Prolonged precoital interval was observed at doses 300 mg/kg/day. No side effect on copulation or fertility were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Pregelatinised maize starch
Croscarmellose sodium
Anhydrous colloidal silica
Magnesium stearate
Tablet coating Opadry II White 85F18422:
- Partially hydrolysed polyvinyl alcohol
- Titanium dioxide (E171)
- Macrogol 3350

- Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC/Al blister, carton.
Pack size: 15, 20, 40, 90, 100 or 120 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

PRO.MED.CS Praha a.s.
Telcska 377/1
Michle
Prague 4
140 00
Czech Republic

8 MARKETING AUTHORISATION NUMBER

PA2179/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th May 2022

10 DATE OF REVISION OF THE TEXT

November 2023