SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PROGIT 50 mg
film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg of itopride hydrochloride.
Excipients with known effect: Each film-coated tablet contains 74.68 mg of lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White to almost white round biconvex scored film-coated tablets, 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, non-ulcer dyspepsia, like feelings of bloating, gastric fullness, discomfort to pain in epigastrium, anorexia, heartburn, nausea and vomiting.
The medicinal product is intended for adults.

4.2 Posology and method of administration

Posology
The recommended dose for adults is 150 mg daily, i.e. 1 tablet 3 times a day before meal. 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. The duration of the administration in clinical studies was maximally 8 weeks.

Paediatric population
The safety and efficacy of itopride in paediatric population has not been established.

Patients with 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.

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Progit 50 mg must 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 side anticholinergic effects.
Data about long-term administration of itopride is not available.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions 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
Safety of itopride in pregnancy was not verified. Therefore itopride can be used in pregnant women or women in that pregnancy cannot be excluded only if therapeutic benefits outweigh possible risks considerably.

Breast-feeding
Data about excretion in mother milk is known only in animals. Because of lack of experience with use of itopride during breast-feeding itopride it is not recommended for breast-feeding women.

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).

Blood and lymphatic system disorders
Uncommon: Leucopenia*.
Not known: Thrombocytopenia.
* Careful observation should be made through haematological examination. The treatment should be discontinued when any abnormality is observed.

Immune system disorders
Not known: Anaphylactoid reaction.

Endocrine disorders
Uncommon: Hyperprolactinaemia**.
Not known: Gynecomastia.
** If e.g. galactorrhea or gynecomastia appeals the treatment must be interrupted or terminated.

Psychiatric disorders
Uncommon: Irritability.

Nervous system disorders
Uncommon: Headache, sleep disorders, dizziness.
Not known: Tremor.

Gastrointestinal disorders
Uncommon: Diarrhoea, constipation, abdominal pain, hypersalivation.
Not known: Nausea.

Hepatobiliary disorders
Not known: Jaundice.

Skin and subcutaneous tissue disorders
Rare: Rash, erythema, pruritus.

Musculoskeletal and connective tissue disorders
Uncommon: Chest or back pain.

Renal and urinary disorders
Uncommon: BUN (blood urea nitrogen) and creatinine increased.

General disorders and administration site conditions
Uncommon: Fatigue.

Investigations
Not known: AST increased, ALT increased, gamma-GTP increased, alkaline phosphatase increased, bilirubin increased.

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 the national reporting system listed in Appendix V.

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.
In animal studies in dogs with a single dose administration itopride supported stomach emptying.
Itopride has high specific action in upper part of gastrointestinal tract.
Itopride does not influence plasma concentrations of gastrin.

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 50 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 ($Vd_{ß}$ = 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

Oral single lethal dose was 2,000 mg/kg in mice and rats and approximately 600 mg/kg in dogs.
Preclinical safety studies were carried out only with doses multiplicatively overrunning therapeutic human doses and found effect have only little importance for use of itopride in humans. In addition to it 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. Nevertheless this was not proved in dogs (dose up to 100 mg/kg/day) and monkeys (dose up to 300 mg/kg/day).
3-month toxicity study in dogs has revealed prostate atrophy after oral administration in dose 30 mg/kg/day. This effect was induced neither after 6-month administration of higher doses (100 mg/kg/day) in rats nor more higher doses (300 mg/kg/day) in monkeys.
Long-term studies of cancerogenity in animals have not been carried out.
In series of *in vitro* and *in vivo* tests no clastogenic and mutagenic effects of itopride were found.
In fertility studies in female rats who were administered doses 30 mg/kg/day and higher hyperprolactinaemia and secondary prolongation of oestral cycle after were observed. Prolonged

precoital interval was observed at doses 300 mg/kg/day. No side effect on copulation and fertility was proved.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Pregelatinised maize starch
Croscarmellose sodium
Silica colloidal anhydrous
Magnesium stearate
Coating composition Opadry II White 85F18422:
- Partially hydrolyzed polyvinylalcohol
- Titanium dioxide (E171)
- Macrogol 4000
- 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

OPA/Al/PVC/Al blister or transparent PVC/PVdC/Al blister, carton.
Pack size: 10, 20, 30, 40, 90 or 100 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]