Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Progit 50 mg film-coated tablets
itopride hydrochloride

PL 37039/0005

PRO.MED.CS Praha a.s.,

LAY SUMMARY

Progit 50 mg film-coated tablets
itopride hydrochloride

This is a summary of the Public Assessment Report (PAR) for Progit 50 mg film-coated tablets. It explains how this product was assessed, and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Progit in this lay summary for ease of reading.

For practical information about using Progit, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Progit and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Ganaton 50 mg tablets.

Progit belongs to a group of drugs called prokinetic agents. Prokinetic agents are drugs which normalise or enhance and accelerate bowel movement (motility). Their administration results in accelerated gastric emptying, accelerated rate of passage of digested food through the small intestine and increased tonus of the lower oesophageal sphincter. In addition, Progit suppresses vomiting.

Progit is indicated for the treatment of symptoms resulting from the slow gastric emptying, such as feeling of gastric fullness up to upper abdominal pain, lack of appetite, heartburn, nausea and vomiting in gastrointestinal disorders, which are not caused by ulcer disease or organic disease affecting the rate of passage of digested food through the gastrointestinal tract.

Progit is intended for adults.

How does Progit work?
Progit contains belongs to a group of drugs called prokinetic agents. Prokinetic agents are drugs which normalise or enhance and accelerate bowel movement (motility). Their administration results in accelerated gastric emptying, accelerated rate of passage of digested food through the small intestine and increased tonus of the lower oesophageal sphincter. In addition, Progit suppresses vomiting.

How is Progit used?
The pharmaceutical form of this medicine is a film-coated tablet, and the route of administration is oral (taken by mouth).

The usual daily dose for adults is 1 tablet three times a day before the meal.

This dose can be reduced according to the course of the disease. The exact dosage of Progit 50 mg and duration of the treatment will be determined by doctor.

For further information on how Progit is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Progit have been shown in studies?
As Progit is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Progit?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

As Progit is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was Progit approved?
It was concluded that, Progit has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Progit?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Progit. The RMP details the important risks of Progit, how these risks can be minimised, any uncertainties about Progit (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Progit.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Progit are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Progit

A marketing authorisation for Progit was granted in the United Kingdom (UK) on 14/06/2024.

The full PAR for Progit follows this summary.

This summary was last updated in September 2024.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Progit 50 mg film-coated tablets (PL 37039/0005) could be approved.

The product is approved for the following indication:

- 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.

The name of the active substance, is itopride hydrochloride, 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 hydrochloride, 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.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Ganaton 50 mg tablets that have been licensed for a suitable time, in line with the legal requirements.

With the exception of an Environmental Risk Assessment, no new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for generic medicinal product of a suitable reference product. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Progit was granted in the United Kingdom (UK) and on 14/06/2024.

II QUALITY ASPECTS

II.1 Introduction

This product contains 50 mg of itopride hydrochloride in each film-coated tablet.

In addition to itopride hydrochloride, this product also contain the excipients lactose monohydrate, pregelatinised maize starch, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate and Opadry II White 85F18422: partially hydrolyzed polyvinylalcohol, titanium dioxide (E171), macrogol 4000 and talc.

The finished product is packaged in polyvinylchloride/polyvinylidene chloride/aluminium blisters in pack sizes of 15, 20, 30, 40, 60, 90, 100 or 120 film-coated tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

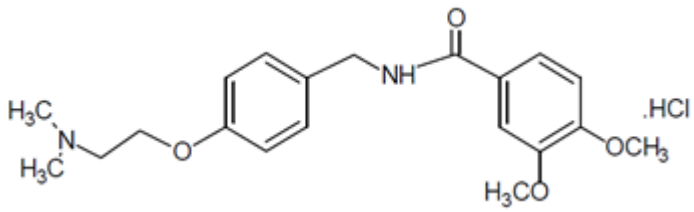
II.2 ACTIVE SUBSTANCE

rINN: Itopride hydrochloride

Chemical Name: Benzamide, N-[{4-(2-dimethyl amino) ethoxy} phenyl methyl]-3,4-dimethoxy hydrochloride

Molecular Formula: $C_{20}H_{26}N_2O_4$**.**HCl

Chemical Structure:



Molecular Weight: 394.89 g/mol

Appearance: White to off white crystalline powder

Solubility: Soluble in water, in dimethyl sulfoxide and in methanol, Practically insoluble in dichloromethane, in hexane, in ethyl acetate and in acetone

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final product. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 5 years, with no special storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of itopride hydrochloride are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for this application

III.4 Toxicology

No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

The Applicant has submitted a preliminary ERA which was conducted using literature search and computational modelling based on the structure of the active substance - itopride hydrochloride. No experimental studies were submitted. While the results of the preliminary analysis are acknowledged, this, exclusively literature and *in silico*, analysis is not in compliance with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2). Therefore, the Applicant has provided a post-authorisation commitment to submit an Environmental Risk Assessment fully compliant with the above-mentioned guidelines within 2 years of the date of issue of marketing authorisation.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of itopride hydrochloride are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study.

Bioequivalence Study 1 (single dose, fasting conditions)

An open-label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover oral bioequivalence study comparing the test product Itoprid PMCS 50 mg film-coated tablets versus the reference medicinal product Ganaton, film-coated tablets in healthy, adult, human subjects under fasting conditions.

The subjects were given a single dose of either treatment with 240 ml of water after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 36 hours after each administration. The washout period between the treatment periods was seven days.

The pharmacokinetic results are presented below:

Table 1: Summary of Itopride's main Pharmacokinetic Parameters

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=31)	REFERENCE (n=31)		LOWER	UPPER
C_{max}	15.8	177.35	164.72	107.67	100.60	115.24
AUC_{0-t}	8.1	615.55	606.37	101.51	98.03	105.12

[a] Units are ng/mL for C_{max} and ng·h/mL for AUC_{0-t}.

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted for this application, and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application, and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION
A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with itopride hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore,

considered to be positive.

The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**