PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GANATON film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg itopride hydrochloride.

Excipients with known effect:

Contains sugar.

Each film-coated tablet contains 35 mg lactose monohydrate.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White, round film-coated tablets with a score on one side and embossed with “HC 803” on the other side.

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 caused by gastric dysmotility and delayed gastric emptying, like sensation of bloating, early satiety, postprandial fullness, upper abdominal pain or discomfort, anorexia, heartburn, nausea and vomiting; functional (non-ulcer) dyspepsia or chronic gastritis.

4.2 Posology and method of administration

The recommended oral adult dose is 150 mg (3 tablets) daily in three divided doses before meals. The dose may be reduced according to patient's age and symptoms.

Duration of Treatment

In clinical studies, itopride hydrochloride has been administered up to 8 weeks.

Paediatric population

GANATON is not indicated for use in children and adolescents under the age of 16 years, as safety and efficacy have 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.

Method of administration

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

4.3 Contraindications

- Hypersensitivity to itopride hydrochloride or to any of the excipients (see section 6.1).
- GANATON 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

Caution is advised as GANATON enhances the action of acetylcholine and may produce cholinergic effects.
GANATON should not be used for extended periods when no improvement of gastrointestinal symptoms is observed. Data on long-term use are not available. GANATON should not be used for more than 8 weeks.

In general, appropriate caution should be exercised in the administration and monitoring of GANATON in elderly patients reflecting the greater frequency of decreased hepatic, renal function, and of concomitant disease or other medicine therapy.

Lactose monohydrate

GANATON contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take GANATON.

4.5 Interaction with other medicines and other forms of interaction

Metabolic interactions are not expected since itopride is primarily metabolized by flavine monooxygenase and not by CYP450.
No changes in protein binding have been seen with coadministration of warfarin, diazepam, diclofenac sodium, ticlopidine hydrochloride, nifedipine, and nicardipine hydrochloride.
Since itopride has gastrokinetic effects, it could influence the absorption of concomitantly orally administered medicines. Particular caution should be taken with medicines with a narrow therapeutic index, sustained release or enteric-coated formulations.
Anti-ulcer medicines like cimetidine, ranitidine, teprenone and cetraxate do not affect the prokinetic action of itopride.

Caution is advised in the concomitant use of GANATON with anticholinergic medicines, as the anticholinergic effect of these medicines may reduce the efficacy of GANATON by inhibiting activation of the gastrointestinal motility.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of use during pregnancy has not been established. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
GANATON should not be used during pregnancy.

Breastfeeding

Itopride is excreted in breast milk of animals, but there is insufficient information on the excretion of itopride in human milk. A risk to the suckling child cannot be excluded, therefore

GANATON is not recommended for use when breastfeeding.

Fertility

No human data on the effect of itopride on fertility are available; however, animal studies do not indicate harmful effects (see section 5.3).

4.7 Effects on ability to drive and use machines

GANATON may cause dizziness. Caution is advised before driving a vehicle or operating machinery until the effects of GANATON are known.

4.8 Undesirable effects

The following undesirable effects have been experienced with the below indicated frequencies in patients in placebo-controlled, reference-controlled, and uncontrolled company sponsored interventional clinical trials with a standard daily itopride dose of 150 mg or lower [common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100)]. No ADRs in the categories very common (≥1/10), rare (≥1/10,000 to <1/1,000), or very rare (<1/10,000) were identified.

Nervous system disorders

Uncommon: dizziness, headache

Gastrointestinal disorders

Common: abdominal pain, diarrhoea

Uncommon: salivary hypersecretion

Skin and subcutaneous disorders

Uncommon: rash

Investigations

Uncommon: alanine aminotransferase increased, white blood cell count decreased

Post marketing experience

The following adverse events have been reported spontaneously during post marketing use.

A precise frequency cannot be estimated from the available data.

Blood and the lymphatic system disorders

Leukopenia, thrombocytopenia.

Immune system disorders

Hypersensitivity, including anaphylactoid reaction.

Endocrine disorders

Blood prolactin increased.

Nervous system disorders

Dizziness, headache, tremor.

Gastrointestinal disorders

Diarrhoea, constipation, abdominal pain, salivary hypersecretion, nausea.

Hepatobiliary disorders

Jaundice.

Skin and subcutaneous tissue disorders

Rash, erythema, pruritus.

Reproductive system and breast disorders

Gynaecomastia.

Investigations

Aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood bilirubin increased.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care

providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Abbott Laboratories South Africa Pharmacovigilance:

pv.south-africa@abbott.com.

4.9 Overdose

There is no specific antidote to GANATON. In case of excessive overdose, symptomatic therapy should be applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 11.10 Other.

Pharmacotherapeutic group: Drugs for functional gastrointestinal disorders, propulsives.

ATC code: A03FA07

Itopride hydrochloride activates gastrointestinal propulsive motility due to its dopamine D_2 antagonizing activity and acetylcholinesterase inhibitory activity. Itopride activates acetylcholine release and inhibits its degradation.

Itopride hydrochloride also has antiemetic action through interaction with D_2 receptors located in the chemoreceptor trigger zone. This was demonstrated by dose dependent inhibition of apomorphine-induced vomiting in dogs.

5.2 Pharmacokinetic properties

Absorption

Itopride hydrochloride is rapidly and almost completely absorbed from the gastrointestinal tract. Relative bioavailability is calculated to be 60 % due to liver first pass metabolism. There is no effect of food on bioavailability. Maximum itopride concentration (C_{max}) is reached after 0,5 to 0,75 hours after administration of 50 mg of itopride hydrochloride.

Distribution

Approximately 96 % of itopride hydrochloride is bound to plasma proteins. Albumin accounts for most of the binding. Alpha-1-acid-glycoprotein accounts for less than 15 % of binding. Itopride distributes into the breast milk of rats.

Biotransformation

Itopride undergoes extensive hepatic metabolism in humans. Three metabolites have been identified, of which only one exerts minor activity without pharmacological relevance (approximately 2 – 3 % of that of itopride). The primary metabolite in humans is the N-oxide, generated by oxidation of the tertiary amine N-dimethyl group.

Itopride is metabolized by a flavin-dependent mono-oxygenase (FMO3). The abundance and efficiency of the human FMO-isozymes can be subject to genetic polymorphisms, which can lead to a rare autosomal recessive condition known as trimethylaminuria (fish odor syndrome). Pharmacokinetics may differ between trimethylaminuria patients and non-trimethylaminuria.

In vivo pharmacokinetic studies on cytochrome P450 (CYP)-mediated reactions revealed that itopride showed neither inhibitory nor inductory effect on CYP2C19 and CYP2E1. CYP content and uridine diphosphate glucuronosyl transferase activity were not altered with the administration of itopride.

Elimination

Itopride hydrochloride and its metabolites are primarily excreted in the urine. The urinary excretions of itopride and its N-oxide were 3,7 % and 75,4 %, respectively, in healthy subjects after oral administration of a single therapeutic dose (50 mg). The terminal phase half-life of itopride hydrochloride was approximately six (6) hours.

Linearity

Following multiple oral doses ranging from 50 mg to 200 mg three times daily, itopride hydrochloride and its metabolites showed linear pharmacokinetics over a treatment period of 7 days, with minimal accumulation.

5.3 Preclinical safety data

Pre-clinical effects were observed only at dosages in excess of human dose indicating little relevance to human use. Moreover, humans are less susceptible to the hormonal effects observed in the animal models.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

In a rat fertility study, prolonged estrous cycle was seen in female animals receiving ≥ 30 mg itopride/kg/day, secondary to hyperprolactinemia. In addition, a prolonged precoital interval was also seen at 300 mg/kg/day. However, the plasma concentrations of itopride in pregnant rats treated orally at 300 mg/kg were about 100-fold higher than the itopride concentrations observed in human serum after clinical administration (50 mg). There was no adverse effect on copulation or fertility. No teratogenic effect was observed in preclinical studies in rats and rabbits, at maternal doses of up to 300 mg/kg

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Maize starch

Carmellose

Colloidal silica anhydrous

Magnesium stearate.

Film-coating:

Hypromellose

Macrogol 8 000

Titanium oxide (E171)

Carnauba wax.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Store at or below 25 °C.

6.4 Special precautions for storage

GANATON does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium foil blister strips, placed in an outer carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott place, 219 Glof Club Terrace

Constantia Kloof 1709

South Africa

8. REGISTRATION NUMBER

56/11.10/0764

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 January 2025

10. DATE OF REVISION OF THE TEXT

N/A