SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Asketon 50mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains itopride hydrochloride 50 mg.
Excipient with known effect: lactose. Each film-coated tablet contains 58.7 mg of lactose (as lactose monohydrate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
White, round, biconvex, film-coated tablets with diameter 7mm.

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
Posology
Adults
The recommended dose of itopride hydrochloride for adult patients is 150mg daily [one tablet (50mg) taken orally three times a day before meals]. The dose may be reduced according to the patient's age and symptoms. (see section 4.4).

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

Method of administration
Oral use. The tablets should be taken before meals.

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Asketon should not be administered to patients in whom increased gastrointestinal motility could be harmful, e.g., in patients with gastro-intestinal bleeding, mechanical obstruction or perforation.

4.4 Special warnings and precautions for use
General
Itopride hydrochloride enhances the action of acetylcholine and may produce cholinergic side effects. Data on long-term use are not available.

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

Geriatric Use
In general, appropriate caution should be exercised in the administration and monitoring of itopride hydrochloride in elderly patients reflecting the greater frequency of decreased hepatic, renal function, and of concomitant disease or other drug therapy (see section 4.2).

Asketon 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 Interaction with other medicinal products and other forms of interaction
- Metabolic interactions are not expected because itopride is mainly metabolised by flavine containing monooxygenases, not by CYP450.
- There are no interactions on the concomitant use of Asketon with warfarin, diazepam, diclofenac, ticlopidine, nifedipine and nicardipine.

- Itopride has gastrokinetic effect, which may affect the absorption of concomitantly orally administrated 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.
- Anti-ulcer medicines such as cimetidine, ranitidine, teprenone and cetrexate do not affect the prokinetic activity of itopride.
- Anticholinergic agents may reduce the action of itopride.

4.6 Fertility, pregnancy and lactation

Fertility

No human data on the effect of Itopride on fertility are available; however, animal studies do not indicate harmful effects of Itopride.

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of itopride in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of itopride during pregnancy.

Breast-feeding

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. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from itopride therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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

The following undesirable effects have been experienced with the below indicated frequencies in 998 itopride-treated patients in 4 placebo-controlled, 4 reference-controlled, and 13 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.

MeDRA SOC	Frequency category	
	Common	Uncommon
Gastrointestinal disorders	Abdominal pain, diarrhoea	Salivary hypersecretion
Investigations		Alanine amino transferase increased, White blood cell count decreased
Nervous system disorders		Dizziness, headache
Skin and subcutaneous tissue disorders		Rash

ADR - 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 lymphatic system disorders

Leukopenia and thrombocytopenia.

Immune system disorders

Hypersensitivity, including Anaphylactoid reaction.

Endocrine disorders

Blood prolactin increased

Nervous system disorders

Dizziness, headache, and tremor.

Gastrointestinal disorders

Diarrhea, constipation, abdominal pain, salivary hypersecretion, and nausea.

Hepato-biliary disorders
Jaundice.

Skin and subcutaneous tissue disorders
Rash, Erythema and Pruritus.

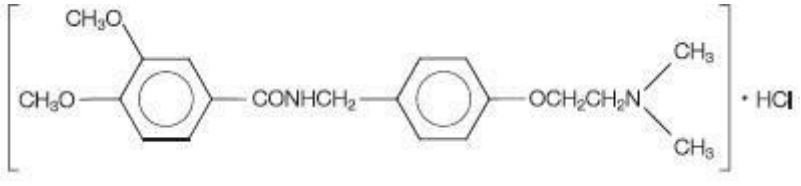
Reproductive system and breast disorders
Gynecomastia.

Investigations
Aspartate aminotransferase increased, alanine aminotransferase increased, Gamma-glutamyl transferase increased, Blood alkaline phosphatase increased and Blood bilirubin increased

4.9 Overdose
Itopride overdose in humans has not been reported. In the case of a large overdose, standard measures are needed, such as gastric lavage and symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for functional gastrointestinal disorders, Propulsives, ATC code: A03FA07

Itopride hydrochloride is an orally active gastroprokinetic agent. Itopride hydrochloride tablets contain 50mg of itopride hydrochloride. The tablet has been formulated to provide immediate release. It is chemically designated as N-[4-[2-Dimethylamino) ethoxy] benzyl]-3,4-dimethoxybenzamide hydrochloride. Itopride hydrochloride is a substituted benzamide. It has an empirical formula of $C_{20}H_{26}N_2O_4$.HCl, molecular weight of 394.89 g/mol, and structural formula as shown:



Mechanism of action
Itopride has dual mechanism of action: dopamine D2 receptor antagonism and acetylcholinesterase inhibition. The effect of itopride is an increase in acetylcholine concentration, which promotes gastric motility, increases the lower oesophageal sphincter (LOS) pressure, accelerates gastric emptying and improves gastroduodenal coordination.

Itopride hydrochloride also has antiemetic action through interaction with D2 receptors located in the chemoreceptor trigger zone. This was demonstrated by dose dependent inhibition of apomorphine induced vomiting in dogs.

In conscious dogs, itopride hydrochloride activates propulsive gastric motility through dopamine D2receptor antagonistic actions and dose-dependent inhibition of acetylcholinesterase.

Itopride hydrochloride has been shown to accelerate gastric emptying in humans, dogs and rats. In single-dose studies in dogs, itopride hydrochloride was shown to promote gastric emptying. The action of itopride hydrochloride is highly specific for the upper gastrointestinal tract.
Itopride hydrochloride does not affect serum gastrin levels.

For functional dyspepsia (FD), the results of 2 placebo-controlled studies revealed statistically significant benefit or clear tendencies for the measured endpoints (Holtmann, 2003 and Yun, 2001). In Holtmann 2003, the symptom severity Leads dyspepsia questionnaire (LDQ) score of the difference between the placebo group and the pooled results of the itopride dose groups (50 mg, 100 mg and 200 mg tid) revealed superiority of itopride ($P<0.05$). Although the test for a dose response was not statistically significant ($P=0.06$) and the difference between placebo and itopride in the 50 mg tid dose revealed $P=0.07$, the other two doses were statistically significant ($P=0.05$). After 8 weeks, overall 41% of the patients receiving placebo were symptom-free or had marked improvement of their motility disorder compared to 57%, 59%, and 64% receiving itopride of 50, 100, or 200 mg tid, respectively ($P<0.05$ for all comparisons). The analysis of the combined endpoint of pain and fullness showed that itopride yielded a greater rate of response than placebo (73% vs. 63%, $P<0.05$). In Yun 2001, the baseline comparison of the symptom scores for motility disorder measured after 2 weeks: itopride (50 mg tid) 89.1%; placebo: 62.5% demonstrated that itopride was better than placebo for subject's global satisfactory evaluation and investigator's global

evaluation, with statistical significance (P<0.05). It showed that itopride was effective in chronic gastritis with dyspepsia.

Overall, the study results of 19 efficacy studies in the category FD showed a positive effect of itopride and patients reported to benefit from itopride treatment. A controlled study of itopride versus mosapride (Amarapurkar 2004), showed a reduction of FD symptoms with both itopride and mosapride treatment and a higher reduction of the severity of symptoms in the itopride group. Statistically significant higher moderate to complete symptom relief was demonstrated with itopride versus metoclopramide (Kamath 1999). In Sawant 1999, patient symptom relief was better for itopride as compared with domperidone.

The results of a meta-analysis of 9 randomized controlled trials enrolling 2,620 FD cases were published by Huang et al. 2012. Compared with control groups (placebo, domperidone, mosapride), itopride had superior relative risk values for global patient assessment, postprandial fullness and early satiety. Itopride improved the LDQ scores more significantly than placebo. The meta-analysis from Wu et al. 2010 of 18 randomized controlled trials in 2,420 subjects showed that the relief rate of anorexia and early satiety in itopride group were statistically superior compared with domperidone.

5.2 Pharmacokinetic properties

Absorption

Itopride is rapidly and almost completely absorbed from the gastrointestinal tract. Relative bioavailability is calculated to be 60 % due to the first pass metabolism. There is no effect of food on bioavailability. Peak plasma levels (Cmax 0.28 g/mL) are reached after 0.5 to 0.75 hours after 50 mg of itopride hydrochloride.

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

Distribution

About 96% of itopride is bound on plasma proteins. Albumin accounts for most of the binding. Alpha-1-acid-glycoprotein accounts for less than 15% of binding.

In rats, itopride is distributed extensively ($V_{d\beta}$ = 6.1 l/kg), with high concentrations in the kidneys, small intestines, liver, adrenal glands, and stomach. Protein binding in the rat was lower than that seen in humans (78 vs 96%). The transfer into the central nervous system, including brain and spinal cord, was minimal. Itopride distributes into the breast milk of rats.

Metabolism

Itopride undergoes extensive hepatic metabolism in humans. Three (3) 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 monooxygenase (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 (TMAU) patients and non-trimethylaminuria (non-TMAU).

In vivo pharmacokinetic studies on CYP-mediated reactions revealed that itopride showed neither inhibitory nor inductor 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 (50mg).

The terminal phase half-life of itopride hydrochloride was approximately six (6) hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate, Carmellose, Pregelatinized maize starch, Silica colloidal anhydrous, Magnesium Stearate.

Film-coating:

Hypromellose 2910, Titanium Dioxide E171, Macrogol 6000, Talc.

6.2 Incompatibilities
Not known.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 30°C in the original package. Protect from light and moisture.

6.5 Nature and contents of container
Itopride tablets are packed in transparent PVC/PVDC-Alu blisters containing 10 tablets. 3x10 blisters or 10 x 10 blisters are packed in a carton box.

6.6 Special precautions for disposal
Avoid release in environment.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Name and address of the manufacturer
Medochemie Ltd. (Central Factory)
1-10, Constantinoupoloes Street, 3011, Limassol, Cyprus

8. Product Registration Holder
Komedic Sdn Bhd
4 Jalan PJS 11/14, Bandar Sunway 46150 Petaling Jaya, Selangor

9. DATE OF REVISION OF THE TEXT
05/2023

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