

GANATON®

ITOPRIDE HYDROCHLORIDE

NAME OF THE MEDICINAL PRODUCTS

Ganaton 50mg tablets

COMPOSITION OF THE MEDICINAL PRODUCT

1 tablet contains 50mg Itopride Hydrochloride

PHARMACEUTICAL FORM

Tablet

CLINICAL PARTICULARS

Indications

Gastrointestinal symptoms in chronic gastritis (bloating feeling, upper abdominal pain, anorexia, heartburn, nausea and vomiting)

Dosage and Administration

The usual adult dosage is 150 mg of itopride hydrochloride (3 tablets) per oral administration daily in three divided doses before meals. The dose may be reduced according to the patient's age and symptoms.

Contraindications

Ganaton is contraindicated in the following patients. Patients with a history of hypersensitivity to any ingredients of this product.

Precautions

Important Precautions

This drug should be used with caution since it enhances the action of acetylcholine. This drug should not be consumed continuously for an extended period when no improvement of gastrointestinal symptoms is observed.

Precautions concerning Use

When granting agent: For drugs packaged in a press-through package (PTP), instruct the patient to remove the drug from the package prior to ingestion. (It has been reported that, by accidental ingestion of the PTP sheet, the hard and sharp corners may puncture the esophageal mucosa, or even lead to perforation resulting in serious complications such as mediastinal sinusitis.)

Drug Interactions

Precautions for coadministration (GANATON should be administered with care when coadministered with the following drugs.)

| Drugs names, etc | Clinical Symptoms /Treatment Procedures | Mechanism and Risk Factors |
|--|---|---|
| Anticholinergic Drugs Tiquizium bromide, scopolamine butyl bromide, timepidium bromide, etc. | Clinical Symptoms: There is a possibility of reducing the action of this product that activates gastrointestinal motility (cholinergic action). | Mechanism: Gastrointestinal motility inhibitory action of Anticholinergic pharmacologically opposes the action of the drug. |

Use during Pregnancy, Delivery or Lactation

This drug should be given to pregnant women and women suspected of being pregnant only when it is considered that the expected therapeutic benefits outweigh the risks. (Safety during pregnancy has not been established.) Ideally, this drug should not be given to women during lactation, but if its administration is required, breast feeding should be avoided. [It has been reportedly excreted in breast milk in an animal study (rats).

Pediatric Use

The safety of this product in children, etc has not been established (There is limited clinical experience).

Use in the Elderly

Since the elderly often have a physiological hypofunction, they are prone to adverse reactions and should thus be closely monitored. If adverse reactions are evident, appropriate measures such as reduction or cessation of the drug should be implemented.

Adverse Reactions

At the approval: Adverse reactions were observed in 14 cases (2.45%) with 19 events (3.32%) of 572 safety assessment intended cases. The major adverse reactions were diarrhea (4 cases, 0.70%), headache (2 cases, 0.35%), abdominal pain (2 cases, 0.35%), etc. Abnormal changes in clinical laboratory test values were Leucopenia (4 cases), increased prolactin (2 cases), etc.

At the end of reexamination: Adverse reactions (including abnormal clinical laboratory test values) were observed in 74 cases (1.25%) with 104 events (1.76%) of 5,913 safety assessment intended cases in the post-marketing surveillance study. The major adverse reactions were diarrhea (13 cases, 0.22%), abdominal pain (8 cases, 0.14%), constipation (8 cases, 0.14%), increased AST (GOT) (8 cases, 0.14%) increased ALT (GPT) (8 cases, 0.14%), etc.

Clinically significant adverse reactions

Shock and anaphylactoid reactions (frequency unknown): Shock and anaphylactoid reactions may occur, and close observation should be made. If hypotension, dyspnoea, larynx edema, urticaria, pallor and diaphoresis etc. occur, the drug should be discontinued and appropriate measures implemented.

Hepatic function disorder and Jaundice (incidence unknown): Hepatic function disorder and jaundice with increased AST(GOT), ALT(GPT) and g-GTP etc., may occur, and close observation should be made. If abnormalities occur, the drug should be discontinued and appropriate therapeutic measures implemented.

Other adverse reactions

| | 5% > ≥0.1% | <0.1% | Incidence unknown¹ |
|---------------------------|---|--|-----------------------------|
| Hypersensitivity² | | | Rash, redness, itching,etc. |
| Extrapryramidal symptoms² | | Tremor, etc. | |
| Endocrine² | | Increased prolactin, etc. | Gynecomastia, etc. |
| Blood (note2) | | Thrombocytopenia, Leucopenia, etc | |
| Gastrointestinal | Diarrhea, constipation, abdominal pain, etc. | Nausea, increased saliva, etc. | |
| Psychoneurologic | | Headache, irritated feeling, sleep disorder, dizziness, etc. | |
| Hepatic | Increased AST (GOT), increased ALT (GPT), etc | Increased γ-GTP, increased Al-P, etc. | |
| Renal | | Increased BUN, increased creatinine, etc. | |
| Others | | Thoracodorsal pain, fatigue | |

Note
1) Incidence is unknown due to spontaneous reports.
2) If any symptom (abnormality) occurs, appropriate measures, such as discontinuing administration, should be considered.

PHARMACOLOGY

Mechanism of action

GANATON enhances the release of acetylcholine (ACh) through dopamine D2-receptor antagonistic action and inhibits the decomposition of released ACh through its acetylcholine esterase (AChE) inhibitory action and exhibits prokinetic effect on gastrointestinal motility by synergism of the same.

Activator Action of the Gastrointestinal Motility

Activation of the gastric motility: The gastric motility in non-anesthetized dogs is activated in a dose-dependent manner.

Activation of the gastric emptying ability: The gastric emptying ability in humans, dogs and rats is activated.

Alleviation of Vomiting: Apomorphine-induced vomiting is inhibited in dogs in a dose-dependent manner.

PHARMACOKINETICS

Serum concentrations

The serum concentrations and pharmacokinetic parameters in healthy adults, after a single oral administration of 50 mg of this drug in the fasting state, are shown in the following Figure and Table.

Figure: Serum concentrations after a single oral administration of 50 mg of the drug(Healthy adults in the fasting state, mean ±S.E.)

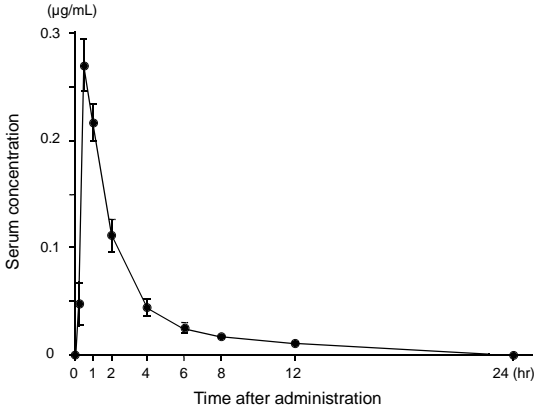


Table: Pharmacokinetic parameters after a single oral administration

| Dose (mg) | Cmax (µg/mL) | Tmax (hr) | AUC _{0-∞} (µg•hr/mL) | T _{1/2β} (hr) |
|-----------|--------------|-----------|-------------------------------|------------------------|
| 50 | 0.28±0.02 | 0.58±0.08 | 0.75±0.05 | 5.77±0.33 |

mean ±SE., n=6

Distribution

(Reference) Results of the Animal Study

The concentrations peaked in almost all tissues at 1 to 2 hours after a single oral administration of 5 mg/kg of ¹⁴C-itopride hydrochloride to rats, while the level at 2 hours after administration was high in the kidneys, small intestines, liver, adrenal glands, and stomach in order of magnitude (high to low) and the transfer into the central nervous system, such as brain and spinal marrow, was minimal.

In intraduodenal administration of 5 mg/kg of ¹⁴C-itopride hydrochloride to rats, the radioactivity concentrations in the gastric muscular layers were about twice as high as those in the blood and there was good distribution into the gastric muscular layers.

Excretion in breast milk: When 5 mg/kg of ¹⁴C-itopride hydrochloride was orally administered to rats, concentrations of radioactivity in breast milk in comparison to serum concentrations of radioactivity were 1.2 times higher in C max, 2.6 times higher in AUC, and 2.1 times higher in T_{1/2}.

Metabolism and Excretion

At a single oral administration of 100 mg of this drug to healthy adults (6 men) in the fasting state, the urinary excretion rate within 24 hours after administration peaked in the N-oxide form [67.54 % of the dose (89.41 % of the urinary excretion)], followed by unchanged compound (4.14%) and the level in other metabolites were minimal. In the experiments using microsomes that express a human CYP or flavine-containing monooxygenase (FMO), it emerged that FMO (FMO1 and FMO3 as molecular species) were involved in the production of the main metabolic N-oxide form. However, no involvement of CYP enzyme (CYP1A2, -2A6, -2B6, -2C8, -2C9, 2C19, 2D6, 2E1, or 3A4) was detected.

4. Others

Serum protein binding ratio: Serum protein binding ratio was 96% after a single oral administration of 100mg of this drug to healthy adults (6 men) in the fasting state.

Pharmaceutical particulars

Incompatibilities

Not applicable.

How supplied

Blister packs of 30 tablets

Date of last revision

May 2008

THIS IS A MEDICAMENT

- Medicament is a product, which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

KEEP ALL MEDICAMENTS OUT OF REACH OF CHILDRENS

Council of Arab Health Ministers Union of Arab Pharmacists

إن هذا دواء

- الدواء مستحضر يؤثر على صحتك، وإستهلاكه خلافاً للتعليمات يعرضك للخطر.
- إتبع بدقة وحقبة الطبيب وطريقة الإستعمال المنصوص عليها وتعليمات الصيدلي الذي صرفها لك.
- الطبيب والصيدلي هما الحيران في الدواء وفي نفعه وضرره.
- لا تقطع مدة العلاج المحددة لك من تلقاء نفسك.
- لا تكرر صرف الدواء بدون وصفة طبية.
- لا تترك الأدوية في متناول أيدي الأطفال.

مجلس وزراء الصحة العرب واتحاد الصيدلة العرب