- CYTOPROTECTIVE
REMEDY FOR GASTRITIS AND GASTRIC ULCER -

GASLON N® Tablets 2mg
GASLON N® Tablets 4mg
GASLON N® Granule 0.8%

<i>Irsogladine maleate preparation</i>

INDICATIONS
Gastric ulcer
Improvement of gastric mucosal lesion (erosion, hemorrhage, redness and edema) caused by the following diseases:
Acute gastritis and acute exacerbation stage of chronic gastritis

DOSAGE AND ADMINISTRATION
For adults, usually 4 mg daily as irsogladine maleate (two tablets of GASLON N® Tablets 2 mg, one tablet of GASLON N® Tablets 4 mg or 0.5 g of GALON N® Granules 0.8% daily) is orally administered in 1 to 2 divided doses. The dose may be adjusted according to the age of patients and severity of symptoms.

PRECAUTIONS
1. Adverse Reactions
Adverse reactions to this drug, including abnormalities in laboratory data, were reported in 64 of 10,176 patients treated (0.63%). The most frequently observed adverse reactions were hepatic function disorder in 12 patients (0.12%), increase in ALT(GPT) in 12 patients (0.12%), increase in AST(GOT) in 7 patients (0.08%), constipation in 6 patients (0.06%), rash in 5 patients (0.05%), pruritus, diarrhea and increase in ALP in each 3 patients (0.03%).

<table>
<thead>
<tr>
<th>Brand name</th>
<th>GASLON N® Tablets 2 mg</th>
<th>GASLON N® Tablets 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>232</td>
<td>233</td>
</tr>
<tr>
<td>Back</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Identification code: 254 (Packet)

*Administration should be discontinued

<table>
<thead>
<tr>
<th>Class</th>
<th>&lt;0.1%-%1%</th>
<th>&lt;0.1%</th>
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</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>constipation, diarrhea, nausea/vomiting</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>The slight increase in AST(GOT), ALT(GPT), ALP and LDH</td>
<td></td>
</tr>
<tr>
<td>Dermatologic*</td>
<td>rash</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>thoracic compression</td>
<td></td>
</tr>
</tbody>
</table>

DESCRIPTION
1. Composition
(1) GASLON N® Tablets 2 mg:
Each tablet contains 2 mg of irsogladine maleate.
(2) GASLON N® Tablets 4 mg:
Each tablet contains 4 mg of irsogladine maleate.
(3) GASLON N® Granules 0.8%:
Each 1 gram contains 8 mg of irsogladine maleate.

2. Product description
GASLON N® Tablets 2 mg:
Plain white round tablets.
GASLON N® Tablets 4 mg:
Plain white round tablets, scored on one side.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>GASLON N® Tablets 2 mg</th>
<th>GASLON N® Tablets 4 mg</th>
</tr>
</thead>
</table>

Identification code: 232

Diameter(mm): 7.0 8.0
Thickness(mm): 2.6 2.7
Weight(mg): 130 170

GASLON N® Granules 0.8%: White granules with slightly sweet taste.
Product identification code: 254 (Packet)

Expired date
Indicated on the package.

<table>
<thead>
<tr>
<th>Storage</th>
<th>Tablets 2mg</th>
<th>Tablets 4mg</th>
<th>Granules 0.8%</th>
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<tbody>
<tr>
<td>Approval No.</td>
<td>(63AM)1139</td>
<td>(63AM)1140</td>
<td>(63AM)1141</td>
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<tr>
<td>Date of listing in the NHI reimbursement price</td>
<td>Dec, 1988</td>
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<td>Date of initial marketing in Japan</td>
<td>Apr, 1989</td>
<td></td>
<td></td>
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<tr>
<td>Date of latest reexamination</td>
<td>Dec, 1996</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of latest approval of indications</td>
<td>Sep, 1994</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Use in the Elderly
Since the elderly often have a physiological hypofunction, it is advisable to take careful administration such as starting by low dose (e.g. 2mg/day) together with enough observing of patients' conditions should be done.

3. Use during Pregnancy, Delivery or Lactation
This product should be administered to pregnant patients or women suspected of being pregnant, only if the expected therapeutic benefit is thought to outweigh any possible risk. (Safety of this drug in pregnant women has not been established)

4. Pediatric Use
Safety in children has not been established. (Adequate clinical studies in children have not been performed.)

5. Precautions concerning Use
Precaution in dispensing: For drugs that are dispensed in press-through package (PTP), instruct the patient to remove the drug from the package prior to use. (It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.)

6. Other Precautions
The elimination half-life from plasma in healthy male subjects is about 150 hours.

PHARMACOKINETICS

1. Absorption
   (1) Single dose administration
   Administered orally 4 mg single dose of irsogladine maleate in 4 healthy male subjects and measured blood concentration on mass fragmentgraphy.

<table>
<thead>
<tr>
<th>tmax</th>
<th>Cmax</th>
<th>half-life</th>
</tr>
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<tbody>
<tr>
<td>3.5hrs</td>
<td>0.154 µg/mL</td>
<td>152hrs</td>
</tr>
</tbody>
</table>

   (2) Chronic administration
   Studied blood concentration with regard to continuous 28 days oral administration of 2mg irsogladine maleate once a day in 6 healthy male subjects.
   The blood concentration started steady after 14 days. The average blood concentration in the 14th and 28th day should be 0.355 ± 0.057 µg/mL and 0.395 ± 0.036 µg/mL, respectively.
   In the 21st day from the final administration, the blood concentration showed 0.05 ± 0.016 µg/mL, and in the 35th day it bellowed threshold limit value(0.05 ± µg/mL).
   Average half-lives were 172 ± 29 hours.

2. Metabolism
   After the oral administration of this drug in healthy male subjects, the major metabolite found in urine is the conjugated form of m-hydroxy irsogladine, and the conjugated form of p-hydroxy irsogladine, and N-oxide of irsogladine are also detected. The pharmacological and toxicological effects of these metabolites are extremely weaker than the unchanged form of irsogladine or are hardly recognized.

3. Excretion
   After the oral administration of 4 mg of irsogladine maleate in healthy male subjects, the cumulative excretion into urine within 80 hours is about 7% and about 20% of the urinary recovery is the unchanged form of irsogladine.

CLINICAL STUDIES

1. Gastric ulcer
   As a result of the clinical trials conducted in patients with gastric ulcer (the disease stage: A_{1}-H_{1}) in 165 domestic institutions, the healing rate by endoscopic evaluation at 8 weeks after the start of administration was 63% (311/497 cases), of all the patients.
   In the overall improvement rating, moderately improved or better evaluations were obtained in 74% (406/546 cases) of all the patients. Efficacy of this product was observed also in the double blind clinical trials.

2. Acute gastritis and acute exacerbation stage of chronic gastritis
   As a result of the clinical trials conducted in patients with acute gastritis or acute exacerbation stage of chronic gastritis in 201 domestic institutions, in the overall improvement rating, moderately improved or better evaluations were obtained in 85% (283/332 cases) of all the patients. Efficacy of this product was observed also in the double blind clinical trials.
### PHARMACOLOGY

1. **Antiulcer effect**
   Irsogladine maleate shows antiulcer effects dose-dependently at a low dose of 1-10 mg/kg in acute experimental ulcers such as water-immersion stress-induced ulcers (in rats\(^{11}\)), ethanol-induced ulcers (in rats\(^{12}\)), Shay ulcers (in rats\(^{13}\)), histamine-induced ulcers (in guineapigs\(^ {14}\), rats\(^{15}\)) and aspirin-induced ulcers (in rats\(^{16}\)) and in chronic experimental ulcers such as acetic acid-induced-ulcers (in rats\(^ {17}\)) and electric thermocauterization ulcers (in dogs\(^ {18}\)).

2. **Cytoprotective effect**
   (1) Pretreatment of irsogladine maleate prevents the desquamation and exfoliation of gastric mucosal epithelial cells and inhibits the expansion of intracellular space induced by intragastric infusion of 0.2N hydrochloric acid (in rats\(^ {19}\)). In the gastric mucosal damage induced by oral administration of absolute ethanol, pretreatment of irsogladine maleate prevents the desquamation and exfoliation of gastric epithelial cells (in rats\(^{20}\)).
   (2) Irsogladine maleate inhibits the penetration of gastric mucosal lesion-inducing substances such as 0.2N hydrochloric acid and ethanol into the gastric mucosa (in rats\(^{21,22}\)).
   (3) Irsogladine maleate increases cyclic-AMP level in gastric mucous cell (in rats\(^{23,24}\)) without affecting gastric mucosal prostaglandin, reduced glutathione and mucousglycoprotein levels (in rats\(^ {25}\)). The cyclic-AMP increasing action of irsogladine maleate in the gastric mucous cell is considered to be related to the cytoprotective effect of this drug.

3. **Increasing action on gastric mucosal blood flow rate**
   Irsogladine maleate increases dose-dependently mucosal blood flow rate at the marginal area of acetic acid-induced ulcer in dogs\(^ {26}\), and the increase of gastric mucosal blood flow rate is also observed in normal rats (the hydrogen gas clearance method).\(^ {27}\)
   Irsogladine maleate also shows an improving effect on the depressed gastric mucosal blood flow induced by norepinephrine or indomethacin in dogs (the heat clearance method with a heated cross-thermocouple flow meter).\(^ {28}\)

4. **Influence on the gastric acid secretion**
   It is observed in the experiment of gastric perfusion of physiological saline that irsogladine maleate dose not affect the basal acid secretion and acid secretion induced by secretagogues (in rats\(^ {29}\)).

5. **Effects on experimental gastritis**
   Irsogladine maleate shows dose dependently suppression or promoting effect of healing on ethanol induced gastritis, taurocholic acid induced atrophic gastritis and ammonia induced gastric mucosa disturbance (in rats\(^ {30}\)).

### PHYSICOCHEMISTRY

#### Nonproprietary name:
- Irsogladine maleate (JAN)
- Irsogladine (INN)

#### Chemical name:
2.4-diamino-6-(2.5-dichlorophenyl)-s-triazine maleate

#### Molecular formula:
\[ C_9H_7Cl_2N_5 \quad \text{ng} \quad C_4H_4O_4 \]

#### Molecular weight:
372.17

#### Structural formula:

![Structural formula](image)

#### Description:
Irsogladine maleate occurs as white crystals or crystalline powder. It is odorless, and has a slightly bitter taste. It is sparingly soluble in 2-methoxyethanol and in glacial acetic acid, slightly soluble in methanol, in ethanol and in acetic anhydride, very slightly soluble in ethyl acetate and in ether, and practically insoluble in water and in chloroform.

#### Melting point:
175-183 °C (decomposition)

#### Partition coefficient:
1.4 [n-octanol (pH1.2)]
54.0 [n-octanol (pH6.8)]
PACKAGING

GASLON N Tablets 2 mg:
Boxes of 100, 500 and 1,000 tablets in press-through package.
Bottles of 500 tablets.

GASLON N Tablets 4 mg:
Boxes of 100, 500 and 1,000 tablets in press-through package.
Bottles of 500 tablets.

GASLON N Granules 0.8%:
0.25g 560 packets, 0.25g 1,680 packets, 0.5g 300 packets
Bottles of 100g and 500g

REFERENCES
7) Unoura M. et al.: Shinyaku To Rinsho 41(11), 2461(1992)
13) Ueda F. et al.: Internal report of Nippon Shinyaku
16) Ueda F. et al.: Internal report of Nippon Shinyaku

REQUEST FOR LITERATURE SHOULD BE MADE TO:
Pharmaceutical Information Center
Nippon Shinyaku Co., Ltd.
14, Nishinosho-Monguchi-cho, Kishshoin, Minami-ku, Kyoto 601-8550, Japan
FAX: (075) 313-7990

INFORMATION ON LONG-TERM ADMINISTRATION
Among the approved indications, the product may be dispensed by prescription for the treatment of gastric ulcer, for 30 days at one time.

Manufactured and Distributed by:
Nippon Shinyaku Co., Ltd.
14, Nishinosho-Monguchi-cho, Kishshoin, Minami-ku, Kyoto 601-8550, Japan