GLYCEOL® Injection

Prescription drug (Note 1)

- INTRACRANIAL PRESSURE REDUCTION AND ANTI-INTRACRANIAL EDEMA AGENT
- INTRAOCULAR PRESSURE REDUCING AGENT--

### Standard Commodity Classification No. of Japan

| 873999, 871319 |

---

**Storage**

Store in a tight (plastic) container at room temperature.

**Precaution**

See the section on “PRECAUTIONS FOR HANDLING”.

**Expiration date**

Use before the expiration date specified on the package.

---

**INDICATIONS**

- Treatment of increased intracranial pressure and intracranial edema
- Improvement of consciousness disorders, neuropathy, and subjective symptoms caused by the improvement of increased intracranial pressure and intracranial edema in the following diseases:
  - Cerebral infarction (cerebral thrombosis, cerebral embolism), intracerebral hemorrhage, subarachnoid hemorrhage, head trauma, brain tumor and cerebral meningitis
  - Postoperative therapy following brain surgery
  - Reduction of brain volume during brain surgery
  - Treatment of increased intraocular pressure
  - Reduction of eyeball volume during eye surgery

**CONTRAINDICATIONS**

GLYCEOL® Injection is contraindicated in the following patients.

1. Patients with congenital glycerin or fructose metabolic disorder

2. Patients with adult-onset type II citrullinemia

**DESCRIPTION**

Combined preparation of glycerin and fructose

<table>
<thead>
<tr>
<th>Brand name</th>
<th>GLYCEOL Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mL</td>
</tr>
<tr>
<td>Approval No.</td>
<td>15400AMZ 00241</td>
</tr>
<tr>
<td>Date of listing in the NHI reimbursement price</td>
<td>Jul 2004</td>
</tr>
<tr>
<td>Date of initial marketing in Japan</td>
<td>May 1979</td>
</tr>
<tr>
<td>Date of latest approval of indications</td>
<td>June 1982</td>
</tr>
<tr>
<td>Date of latest reexamination</td>
<td>Jan 1988</td>
</tr>
</tbody>
</table>

**INDICATIONS AND ADMINISTRATION**

The usual adult dosage for intravenous drip infusion is 200-500 ml once or twice daily, to be administered over a 2-3 hour period for 500 ml.

As a general rule, the duration of administration is one to two weeks.

The dosage may be adjusted according to the patient’s age and symptoms.

In order to reduce the brain volume during brain surgery, 500 ml of this product is drip infused over a 30-minute period.

In order to reduce intraocular pressure or eyeball volume during eye surgery, 300-500 ml of this product is drip infused over a 45-90 minute period.

---

**Note 1)** Caution - Use only pursuant to the prescription of a physician, etc.

**Note 2)** concentration of 0.9 w/v%: See the section on “PRECAUTIONS”.

---

**CONTRAINdications (GLYCEOL® Injection is contraindicated in the following patients.)

1. Patients with congenital glycerin or fructose metabolic disorder
   
2. Patients with adult-onset type II citrullinemia
PRECAUTIONS
1. Careful Administration (GLYCEOL® Injection should be administered with care in the following patients.)
   (1) Patients with cardiac or circulatory dysfunction [An increase in the volume of the circulating blood puts more stress on the heart, which in turn may exacerbate symptoms.]
   (2) Patients with renal dysfunction [Water and sodium chloride tended to be administered excessively, which may exacerbate symptoms.]
   (3) Patients with diabetes insipidus [Electrolyte management is required for patients with this disease, and the administration of this product may effect the balance of electrolytes, thus exacerbating symptoms.]
   (4) Patients with diabetes [Hyperosmolar nonketotic coma may occur.]

2. Important Precautions
   (1) Neurological disorders (convulsion, tachypnoea, lethargy, etc.) leading to death has been reported of neonates, sucklings and infants with fructose 1,6-bisphosphatase (FBPase) deficiency who received Glyceol for brain oedema or prevention of metabolic failure-induced brain oedema. When the drug is used for treatment of brain oedema or consciousness disturbance of unknown origin in neonates, etc., the blood glucose and lactate levels should be measured. The drug should not be used in patients with abnormal gluconeogenesis, especially in those suspected to have FBPase deficiency. Furthermore, it should be confirmed during and after the treatment that no decreasing tendency is observed in the blood glucose level and that no aggravation is seen in brain oedema as well as in neurological symptoms represented by consciousness disturbance. If any aggravation is confirmed, administration of the drug to these patients should be discontinued.
   (2) There has been a reported case of adult-onset type II citrullinemia in which the patient’s condition was aggravated following administration of this product for treatment of cerebral edema, and death ensued. This product should not be administered if adult-onset type II citrullinemia (a disorder with elevated blood citrulline, characterized by abnormal behavior and disturbance of consciousness due to recurring hyperammonemia) is suspected.
   (3) To those patients who are suspected of having an acute sub- or epidural hematoma, this product should be administered only after adequate treatment to the source of bleeding and upon confirming that there is no hazard of re-bleeding (If this product is administered without confirming existence of hematoma, a decrease in intracranial pressure is likely to result in re-bleeding.)
   (4) Since this product contains sodium chloride, it should be administered with care in patients for whom salt-intake should be restricted.
   (5) Since lactic acidosis may occur, this product should be administered with care.

3. Adverse Reactions
   One hundred and eighty-four (184) adverse reactions to this product were reported in 157 (1.82%) of 8,650 patients treated (at the end of the reexamination, 1988). (1) Clinically significant adverse reactions
   Acidosis (incidence unknown): Lactic acidosis may occur.: If the symptoms are observed, appropriate measures such as, the administration of sodium bicarbonate injection, should be taken (voluntary revision, 1995).
   (2) Other adverse reactions
   When the following adverse reactions are observed, appropriate measures such as dosage discontinuation should be taken.

<table>
<thead>
<tr>
<th>Adverse reaction /incidence</th>
<th>5% &gt; ≥0.1%</th>
<th>&lt;0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary</td>
<td>Occult blood in urine, Hemoglobinuria, Hematuria, Micturition</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Retching</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>Hypokalemia, Hyperkalemia, Hyperosmolar nonketotic Hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Headache, Thirst</td>
<td>Arm pain, Increased blood pressure, Malaise</td>
</tr>
</tbody>
</table>

4. Use in the Elderly
   Since the elderly often have reduced physiological function, this product should be administered with care while paying attention to abnormalities of water and electrolyte levels.

5. Precautions concerning Use
   Precautions prior to administration
   (1) Since patients may have a desire to urinate during eye surgery, they should be instructed to urinate before surgery.
   (2) When administering this product, appropriate measures should be taken to prevent infections (e.g., sterilizing patient’s skin and equipment).
   (3) When outside temperature is low, this product should be warmed to body temperature before use.
   (4) This product should be used immediately once the seal is broken, and any residual product must be discarded.

PHARMACOKINETICS
1. Distribution (reference):
   The results of autoradiography following the intravenous administration of 14C-glycerin to rats showed that radioactivity was detectable in almost every part of the body. Even though radioactivity disappeared quickly from the blood and liver, it took longer for the radioactivity to reach the brain and hence to disappear from it.

2. Metabolism and excretion (reference):
   14C-glycerin was administered intravenously to rats and rabbits. The results showed that 65% of the administered radiation was excreted as 14CO2 in expired air within 48 hours. The urinary excretion of 14C-glycerin in rats and
rabbits was 13% and 9%, respectively, but its fecal excretion was very low in both rats and rabbits. Also, the biliary excretion of this compound was 1% or less.

**CLINICAL STUDIES**

1. A double-blind comparative study was conducted on 61 patients with persistently high intracranial pressure and intracerebral edema. When 500 ml of this product was administered intravenously over a two-hour period, the intracranial pressure rapidly decreased, the intracranial edema alleviated, and the cerebral blood flow improved. Also, subjective and objective symptoms improved, thus the clinical usefulness of this product was demonstrated\(^5\). The overall clinical improvement rate (third-party assessment) (better than “improved”): 41.4% (12/29)

2. To patients with various central nervous system diseases accompanied by intracranial edema or increased intracranial pressure (253 patients at 17 medical institutions), 500-1,000 ml/day of this product was administered intravenously. The results showed that the cerebrospinal pressure significantly decreased, and subjective and objective symptoms associated with increased intracranial pressure improved in 61.7% of these patients\(^6\).

3. A double-blind comparative study was conducted on 57 patients with glaucoma or those who received preoperative therapy for glaucoma and cataracts. When 500 ml of this product was administered intravenously over a 60-90 minute period, its clinical usefulness was demonstrated\(^7\). Usefulness rate (better than “Useful”): 87.7% (50/57)

**PHARMACOLOGY**

1. The intravenous administration of glycerin to cats and rabbits significantly reduced their cerebrospinal pressure\(^8\).

2. The intravenous administration of this product to rabbits decreased the internal pressure of the anterior sac and vitreum\(^9\).

3. This product was administered intravenously to canine encephalopathy models induced by the epidural balloon and cold-injury methods. The results showed that elevated levels of cerebral water decreased, and cerebral blood flow, cerebral oxygen consumption, and cerebral tissue metabolism increased\(^10\).

4. Physiological and histological examinations were conducted by intravenously administering this product to experimentally induced cerebral ischemia feline models. The results confirmed that this product protects against cerebral ischemia\(^11,12\).

5. The intravenous administration of this product to patients, with increased intracranial or intraocular pressure, rapidly and significantly reduced the intracranial or intraocular pressure\(^5,7,13,14\).

6. This product or glycerin was administered to patients with cerebral apoplexy. The measurement of regional cerebral blood flow showed an increase in the blood flow from an ischemic to normal state, and redistribution of the blood from congested areas to ischemic areas\(^15-17\).

7. Free fatty acid is believed to block energy production in cerebral cells, which leads to a vicious circle of intracranial edema formation. The administration of glycerin to patients with cerebral apoplexy decreased the level of free fatty acid, thus confirming that glycerin is involved in brain metabolism\(^16,18,19\).

**PRECAUTIONS FOR HANDLING**

1. Insert an injection needle perpendicularly into the rubber stopper through the circle mark. If inserted at an angle, the needle may penetrate the neck wall of the container and cause leakage of the fluid.

2. As the soft bag products cannot be administered by the tandem system with a coupling tube (U-shaped tube), use a Y-type infusion set when simultaneous or continuous administration of two soft bags is intended.

3. Do not use this product if water drops are seen inside the container or the contents appear opaque or pigmented.

4. The scale shown on each container should be used as a guideline.

**PACKAGING**

- **200 mL Injection**
  - 10 Bags (10 bags × 1), 20 Bags (5 bags × 4)

- **300 mL Injection**
  - 10 Bags (10 bags × 1), 20 Bags (5 bags × 4)

- **500 mL Injection**
  - 10 Bags (10 bags × 1), 20 Bags (5 bags × 4)

**REFERENCES**


REQUEST FOR LITERATURE SHOULD BE MADE TO:
Medical Information Department
Chugai Pharmaceutical Co., Ltd.
1-1 Nihonbashi-Muromachi 2-chome, Chuo-ku, Tokyo 103-8324, Japan
Tel: 0120-189706
Fax: 0120-189705
http://www.chugai-pharm.co.jp

Manufactured & Sold by:
Chugai Pharmaceutical Co., Ltd., Roche Group
1-1 Nihonbashi-Muromachi 2-chome, Chuo-ku, Tokyo 103-8324, Japan