- Synthetic salmon calcitonin preparation -

**CALCITORAN® for Injection**

<Calcitonin Salmon (Synthesis)>

**Storage**
Store at room temperature.

**Expiration date**
Do not use after the expiration date indicated on the package.

### CONTRAINDICATIONS (CALCITORAN for Injection is contraindicated in the following patients.)
Patients with a history of hypersensitivity to the product.

### DESCRIPTION

<table>
<thead>
<tr>
<th>Brand name</th>
<th>CALCITORAN for Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>Each 1 mL ampule contains 10 IU of calcitonin salmon (synthesis)</td>
</tr>
<tr>
<td>Product description</td>
<td>Ampule (lyophilized preparation with white lumps or powder)</td>
</tr>
<tr>
<td>Inactive ingredient</td>
<td>Each 1 mL ampule contains 10 mg of lactose</td>
</tr>
<tr>
<td>Attached solvent</td>
<td>1 mL ampule of physiological saline (sodium chloride and water for injection) is attached for one ampule.</td>
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</tbody>
</table>

When one ampule is dissolved by attached solvent, the solution is colorless and transparent.

pH: 4.0-6.0
Osmotic pressure: About 1 (ratio against physiological saline)

The activity of calcitonin salmon (synthesis) is determined by bioassay based on WHO's international reference preparation, “International Reference Preparation of Calcitonin, Salmon for Bioassay,” and expressed as international units (IU).

### INDICATIONS
Pain in osteoporosis.

### DOSAGE AND ADMINISTRATION
Before use, one ampule is dissolved by attached solvent. Usually for adults, 1 ampule (10 IU as calcitonin salmon (synthesis)) is intramuscularly administered twice a week. The dosage may be adjusted depending on the symptoms.

### PRECAUTIONS

1. **Careful Administration (CALCITORAN for Injection should be administered with care in the following patients.)**
   - (1) Patients with a predisposition to hypersensitive reaction such as rash or urticaria
   - (2) Patients with bronchial asthma or with a history of bronchial asthma
     [Asthmatic attack may be induced.]

2. **Important Precautions**
   - (1) The drug is a polypeptide preparation and may cause shock. The patient should be carefully inquired as to the history of allergy and drug hypersensitivity. Intradermal test is recommended prior to use.
   - (2) Since an increase in the incidence of pituitary tumor was reported in the repeated dose toxicity in which high dose of calcitonin salmon (synthesis) were subcutaneously administered to rats for one year, the drug should not be given carelessly for a long period of time.

3. **Drug Interactions**

   **[Precautions for coadministration] (CALCITORAN for Injection should be administered with care when coadministered with the following drugs.)**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates (Inhibitor of bone resorption: Pamidronate disodium, etc.)</td>
<td>Serum calcium level may rapidly decrease³. In case of severe hypocalemia associated with clinical symptoms, the treatment with the drug should be discontinued, and proper treatment such as calcium injection should be performed.</td>
<td>By coadministration, hypocalcemic action may be increased.</td>
</tr>
</tbody>
</table>
4. Adverse Reactions
Of the 7,264 patients investigated in the clinical trials and at post-marketing survey of CALCITORAN Injection 10, 129 patients (1.78%) developed adverse reactions, including abnormal laboratory values, were reported. Major findings are: increased BUN (0.19%), facial hot flushes (0.17%), nausea (0.14%), increased GPT (0.10%) (as of the end of reexamination).

(1) Clinically significant adverse reactions
Since shock (incidence unknown) may occur, patients should be carefully observed, and the treatment with the drug should be discontinued in the event of symptoms such as discomfort, paresthesias of the mouth, wheezes, vertigo, desire of defecation or tinnitus.

(2) Clinically significant adverse reactions (by similar drugs) (incidence unknown)
1) Since hypocalcemic tetany induced by similar drug (elcatonin) has been reported, the treatment with the drug should be discontinued, and proper treatment such as calcium injection should be performed in the event of such symptoms.
2) Since asthmatic attack induced by similar drug (elcatonin) has been reported, the treatment with the drug should be discontinued, and proper treatment should be performed in the event of such symptoms.

(3) Other adverse reactions

<table>
<thead>
<tr>
<th>Incidence</th>
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<tbody>
<tr>
<td>5%&gt;20.1%</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Hypersensitivity†</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Psychoneurologic</td>
</tr>
<tr>
<td>Hepatic</td>
</tr>
<tr>
<td>Electrolytes</td>
</tr>
<tr>
<td>Site of injection</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>

[Note]† In such cases, proper treatment such as the discontinuation of the drug should be performed.

5. Use in the Elderly
Since elderly patients often have reduced physiological function, careful supervision and measures such as reducing the dose are recommended.

6. Use during Pregnancy, Delivery or Lactation
The drug should be used in pregnant women and women who may be pregnant only if the expected therapeutic benefits outweigh the possible risk associated with treatment.

[The safety of this drug in pregnant women, parturient women and nursing mothers has not been established. It is reported that, when the drug was administered to animals (rats) during the pregnancy and lactation period, suppressed weight gain of newborns due to the decrease of milk secretion was observed. Also it is reported that the tetany-like symptoms occurred in dams at the late phase of pregnancy period, which was associated with sudden decrease in serum calcium.]

7. Pediatric Use
Safety of this drug in children has not been established. (There is insufficient clinical data in pediatric patients).

8. Precautions Concerning Use
(1) Dissolve
Use immediately after dissolving.

(2) Intramuscular injection
The following cautions should be taken in intramuscular administration:
1) Avoid repeated injections at the same site. Exercise the caution particularly in children.
2) Do not inject at innervated sites.
3) If insertion of the injection needle evokes intense pain, or if blood flows into the syringe, withdraw the needle immediately and inject at a different site.

(3) Others
The product is supplied as one-point-cut ampules. The cut point of the ampule should be wiped with an alcohol swab, etc., before opening.

PHARMACOKINETICS
When 20 IU of the drug was intramuscularly administered to healthy adults, T<sub>max</sub>, C<sub>max</sub>, T<sub>1/2</sub>, and AUC were 23.25±10.42 (min), 24.50±7.79 (pg/mL), 41.96±18.34 (min), and 1829.26±1103.87 (pg·min/mL), respectively.
[Note] The approved dose of the drug is 10 IU.

CLINICAL STUDIES
In open labeled clinical trials in patients with osteoporosis received the drug 10 IU/dose twice weekly for 4 weeks, the rate of overall improvement and overall usefulness, using pain as an index of improvement, were 73.3% (33/45) and 68.6% (35/51), respectively.

PHARMACOLOGY
1. Effects on experimental osteoporosis<sup>2,3</sup>
In rats with experimental osteoporosis (induced by ovariectomy and feeding low-calcium diet, and by renal subtotal resection), calcitonin salmon (synthesis) improved bone strength and bone calcium content.

2. Effects on bone-protecting factors<sup>4</sup>
Calcitonin salmon (synthesis) suppressed urinary calcium excretion in the experimental model (rat) in which the change in filtrated load of calcium at the proximal tubules of kidney associated with its hypocalcemic action is adjusted.
In vitamin D-deficient and thyroparathyroid-ectomized rats, calcitonin salmon (synthesis) increased the conversion of 25(OH)-D₃ to 1,25(OH)₂-D₃ in the kidney. With these two actions, calcitonin salmon (synthesis) kept a positive calcium balance in the body.

3. Hypocalcemic effect associated with suppression of bone resorption

In various animal species (mice, rats, guinea pigs, rabbits and dogs), calcitonin salmon (synthesis) suppressed bone resorption, leading to continuous decrease in serum calcium level.

PHYSICOCHEMISTRY

Nonproprietary name:
Calcitonin salmon (synthesis) (JAN)
Calcitonin (INN)

Molecular formula:
C₁₄₅H₂₄₀N₄₄O₄₈S₂

Structural formula:

Molecular weight:
3431.88

Description:
Calcitonin salmon (synthesis) occurs as hygroscopic, white powder. It is odorless or has a faint smell of acetic acid. It is very soluble in water and practically insoluble in acetonitrile, ethanol or ether.

PACKAGING

CALCITORAN for Injection:
Boxes of 10 ampules (10 ampules of physiological saline (1 mL) are attached as solvent)
Boxes of 50 ampules (10 ampules of physiological saline (1 mL) are attached as solvent)

REFERENCES


REQUEST FOR LITERATURE SHOULD BE MADE TO:
Medical Service Department
Teikoku Hormone Mfg. Co., Ltd.
5-1, Akasaka 2-chome, Minato-ku, Tokyo, 107-8522 Japan

Manufactured by:
Teikoku Hormone Mfg. Co., Ltd.