Revised: January 2014 (11th version)

Standard Commodity Classification No. of Japan
872329

- Gastritis and gastric ulcer treatment -

Selbex® Capsules 50mg
Selbex® Fine Granules 10%

<Teprenone preparation>

Storage
SELBEX should be stored at room temperature. Bottle packages of fine granules should be stored with protection from light after opening the cap or the aluminum bag. (Exposure to light may result in decrease in content of the medicine.)

	Capsules	Fine granules
Approval No.	15900AMZ01060000	15900AMZ01061000
Date of listing in the NHI reimbursement price	Nov 1984	Nov 1984
Date of initial marketing in Japan	Dec 1984	Dec 1984
Date of latest reexamination	Dec 1991	
Date of latest approval of indications	Aug 1988	

Expiration date
SELBEX should be used before the expiration date indicated on the package or label.

Caution in dispensing: See "PRECAUTIONS FOR HANDLING" section.

DESCRIPTION

1. Composition

Capsules 50 mg:

Each hard capsule with an opaque grayish blue-green cap and opaque light orange body contains 50 mg of teprenone. It also contains FD&C Yellow No.6 (Sunset Yellow FCF), hydrated silicon dioxide, glycine, FD&C Blue No.1 (Brilliant Blue FCF), gelatin, talc, corn starch, tocopherol, macrogol 6000, D-mannitol and sodium lauryl sulfate as inactive ingredients.

Fine Granules 10%:

Each gram of white to yellowish white granules contains 100 mg of teprenone.

It also contains hydrated silicon dioxide, talc, tocopherol, lactose hydrate, hydroxypropylcellulose and D-mannitol as inactive ingredients.

2. Product description

Brand name	Dosage form and identification code	Appearance	Description
SELBEX Capsules 50 mg	Hard Capsules		Capsules Cap: Opaque grayish blue-green Body: Opaque light orange Contents: White to yellowish white, granules or powder
	SX50∈	Length (mm) 14.3 / Weight (mg) 160 / Size No.4	
SELBEX Fine-granules 10%	Fine granules		White to yellowish white

INDICATIONS

- Improvement of gastric mucosal lesions (erosion, hemorrhage, redness and edema) in the following diseases:
  Acute gastritis and acute exacerbation stage of chronic gastritis
- Gastric ulcers

DOSAGE AND ADMINISTRATION

Capsules 50 mg:

The usual adult dosage for oral use is 3 capsules (150 mg of teprenone) daily in three divided doses after meals. The dosage may be adjusted depending on the patient's age and symptoms.

Fine Granules 10%:

The usual adult dosage for oral use is 1.5 g (150 mg of teprenone) daily in three divided doses after meals. The dosage may be adjusted depending on the patient's age and symptoms.

PRECAUTIONS

1. Adverse Reactions

Adverse reactions were reported in 52 of 10,914 patients (0.48%). (At the end of the reexamination period)

(1) **Clinically significant adverse reactions** (incidence unknown)

Hepatic function disorders and jaundice

Hepatic function disorders accompanied by elevation of AST (GOT), ALT (GPT), γ-GTP or Al-P, or jaundice may occur. In the event of such abnormal findings, administration should be discontinued and appropriate measures should be taken.

(2) **Other adverse reactions**

	5% > ≥0.1%	<0.1%	Incidence unknown
Gastrointestinal		Constipation, diarrhea, nausea, thirst, abdominal pain and feeling of enlarged abdomen	
Hepatic	Elevation of AST (GOT) and ALT (GPT)		
Psychoneurologic		Headache	
Hypersensitivity note)		Rash and itching	
Others		Elevation of total cholesterol and redness/feeling of warmth in eyelids	thrombocytopenia

Note) In the event of such symptoms, treatment should be discontinued.

2. Use in the Elderly

Since the elderly often have a physiological hypofunction, it is advisable to take measures, such as reduction in dosage under careful supervision.

3. Use during Pregnancy, Delivery or Lactation

SELBEX should only be used for pregnant women or women suspected of being pregnant, if the expected therapeutic benefits are evaluated to outweigh the possible risk of treatment.

[The safety of SELBEX has not been established in pregnant women.]

4. Pediatric Use

The safety in children has not been established (insufficient clinical experience).

5. Precautions concerning Use

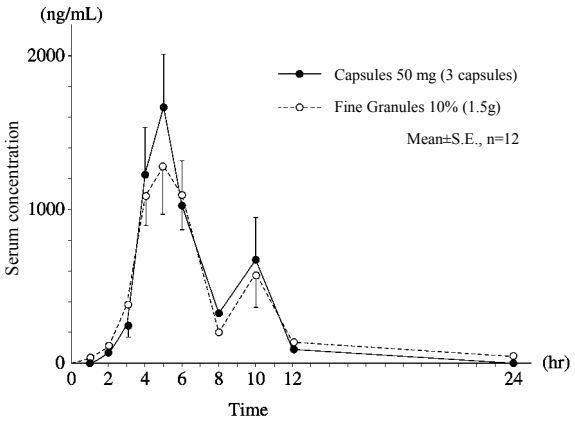
Caution in handing over drug (capsules)

For drugs that are dispensed in a 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, causing perforation and resulting in serious complications such as mediastinitis.]

PHARMACOKINETICS

1. Blood concentration

Three capsules of SELBEX Capsules or 1.5 g of SELBEX Fine Granules 10% (150 mg note) of teprenone) were administered orally to twelve healthy adult male volunteers after a meal in a crossover design. The serum teprenone concentrations were determined and are shown in the following figure. The maximum drug concentration (C_{max}) and the area under the plasma concentration curve ($AUC_{0\text{-}32}$) are shown in the following table. There was no significant difference in C_{max} or $AUC_{0\text{-}32}$ between the 2 dosage forms.



Serum teprenone concentration after oral administration at a single dose of 150 mg note) of teprenone

Pharmacokinetic parameters after oral administration at a single dose of 150mg note) of teprenone

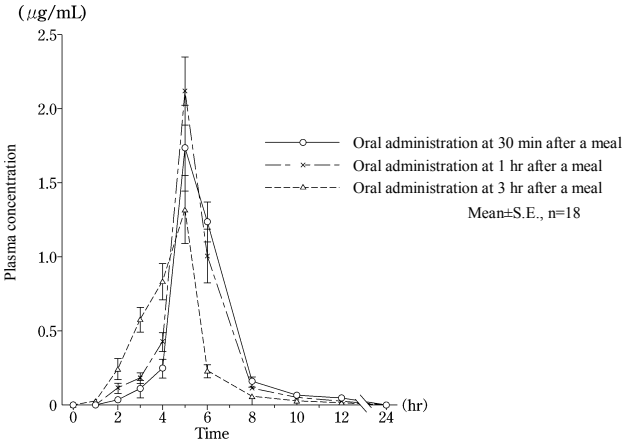
Forms	$AUC_{0\text{-}32}$ (μg·hr/mL)	C_{max} (μ/mL)
SELBEX Capsules 50mg (3 capsules)	7.831±0.822	2.195±0.312
SELBEX Fine Granules 10% (1.5g)	7.055±0.657	1.919±0.253

(Mean±S. E., n=12)

Note) A single oral dose of 150 mg is unapproved.

2. Effect of meal

Three capsules of SELBEX Capsules (150 mg note) of teprenone) were administered orally to eighteen healthy adult male volunteers at 30 min, 1 hr or 3 hr after a meal in a cross-over design. The plasma teprenone concentrations were determined and are shown in the following figure and table. The area under the plasma concentration-time curve (AUC) at 30 min after a meal is comparable with that at 1 hr after a meal. The AUC at 3 hr after a meal was 23 % lower than that at 30 min after a meal. [1)]



Plasma teprenone concentration after oral administration at a single dose of 150mg note) of teprenone

Pharmacokinetic parameters of teprenone

	$AUC_{0\text{-}24}$ (μg · hr/mL)	C_{max} (μg /mL)	t_{max} (hr)
30 min after a meal	4.768 ± 1.368	2.087 ± 1.041	5.4 ± 0.5
1 hr after a meal	4.858 ± 1.434	2.274 ± 0.930	5.1 ± 0.6
3 hr after a meal	3.671 ± 1.296	1.562 ± 0.852	4.3 ± 0.9

(Mean±S.D., n=18)

Note) A single oral dose of 150 mg is unapproved.

CLINICAL STUDIES

Clinical efficacy

(1) It has been demonstrated that SELBEX was useful for acute gastritis and acute exacerbation stage of chronic gastritis in a double blind clinical trial. The overall efficacy rate of SELBEX for patients with gastritis was 68.6% (448/653). [2)]

(2) SELBEX was found to be effective in 81.0% (438/541) of patients with gastric ulcers. It has been demonstrated that SELBEX was particularly useful for the treatment of peptic ulcers in the elderly, large size ulcers and recurrent ulcers, etc. in a double-blind clinical trial. [3)]

PHARMACOLOGY

1. Anti-ulcer effect

Teprenone has been demonstrated to show a potent anti-ulcer effect against various experimental ulcers in rats (caused by cold-restraint, indomethacin, aspirin, prednisolone, reserpine, acetic acid, thermocautery or aspirin-cold-restraint) and to be very effective against various experimental gastric mucosal lesions (caused by hydrochloric acid, aspirin, ethanol or radiation). [4 - 7)]

Further, in an experiment using rats, teprenone has been demonstrated to inhibit gastric mucosal lesions due to compound 48/80 or platelet activating factor (PAF) in which active oxygen is thought to be involved. [8, 9)]

2. Increase of gastric mucus

Teprenone promotes mucus synthesis and secretion in cultured gastric mucosal epithelial cells of rat origin. [10)]

When present in the superficial mucous cells and neck cells, teprenone increases the output of mucus from these cells in rats. [11, 12)]

Teprenone increases activities of synthetases mediating the biosynthesis of high-molecular glycoprotein in rats and phospholipids in guinea pigs, the main factors for gastric mucosal regeneration and protection, and promotes the synthesis and secretion of high-molecular glycoprotein and phospholipids in rats and humans. [13 - 16)]

In addition, it has also been demonstrated in rats and rabbits that teprenone increases the bicarbonate content of the gastric mucus. [17)]

3. Cytoprotect effect due to induction of heat shock proteins (HSP) genesis

Teprenone induces genesis of HSP60, 70, 90 in gastric mucosal cells and shows cytoprotect effect in guinea pigs. [18)]

4. Increase of gastric mucosal prostaglandins

Teprenone increases the content of prostaglandin E_2 and I_2 in the gastric mucus of rats. In rats, the mechanism for this has been demonstrated to be an increase in prostaglandin synthetase activity. [19, 20)]

5. Increase and improvement of gastric mucosal blood flow

Teprenone increases gastric mucosal blood flow in humans. Teprenone rectifies the decrease in gastric mucosal blood flow in water-immersion restrained rats. [21, 22)]

6. Protection of the gastric mucosa

Teprenone inhibits ethanol-induced injury of the gastric mucosa in rats. [23)]

Teprenone inhibits ethanol-induced injury of the gastric mucosa in healthy adult male volunteers. [24)]

7. Maintenance of the homeostasis of the gastric mucosal-cell proliferation zone

Teprenone enhances gastric mucosal cell proliferation which has been reduced by hydrocortisone in mice, thus helping to maintain the homeostasis of the gastric mucosal cell proliferation zone. Teprenone promotes gastric mucosal regeneration and injured gastric mucosal repair in acetic acid ulcers in rats. [25, 26)]

8. Inhibition of lipid peroxidation

Teprenone inhibits both gastric mucosal injury due to burning as well as increases in lipid peroxide levels in the gastric mucosa in rats. [27)]

PHYSICOCHEMISTRY

Nonproprietary name: Teprenone (JAN, INN)

Chemical name:

(5*E*,9*E*,13*E*)-6,10,14,18-Tetramethylnonadeca-5,9,13,17-tetraen-2-one

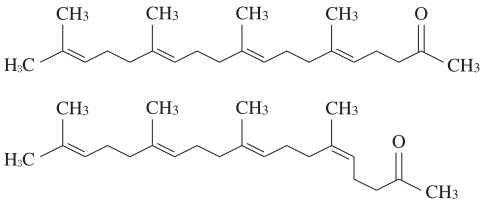
(5*Z*,9*E*,13*E*)-6,10,14,18-Tetramethylnonadeca-5,9,13,17-tetraen-2-one

2:3 (5*Z*,5*E*) geometrical mixture of mono-cis and all trans forms.

Molecular formula: $C_{23}H_{38}O$

Molecular weight: 330.55

Structural formula:



Description:

Teprenone occurs as a colorless to pale yellow clear, oily liquid. It has a slight characteristic odor.

It is miscible with ethanol (99.5%), ethyl acetate, and hexane and practically insoluble in water. It oxidizes in air, gradually yellowing.

Refractive index : n_D^{20} : 1.485-1.491

Specific gravity : d_{20}^{20} : 0.882-0.890

PRECAUTIONS FOR HANDLING

The fine granules turn yellow and their teprenone content is gradually decreased when combined with synthetic alminum silicate. Therefore, they should not be combined directly with this substance.

PACKAGING

SELBEX Capsules 50 mg:

Boxes of 100, 210 (21 Caps. × 10), 1,000, 1,050 (21 Caps. × 50), 3,000 and 3,150 (21 Caps. × 150) in press-through packages, and bottles of 500 and 3,000

SELBEX Fine Granules 10%:

Bottles of 100 g, 500 g, 1 kg, 3 kg and 5 kg, and boxes of 105 g (0.5 g packet × 3 × 70), 630 g (0.5 packet × 3 × 420) and 3.15 kg (0.5 g packet × 3 × 2,100)

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