Revised: July 2009 (10th version)

Standard Commodity Classification No. of Japan
871249

- For improvement of myotonic symptoms -

Myonal® Tablets 50 mg
Myonal® Granules 10 %

<Eperisone hydrochloride preparation>

Prescription drug

Storage
MYONAL should be stored at room temperature. MYONAL should be protected from moisture after opening package.

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

	Tablets 50 mg	Granules 10 %
Approval No.	15700AMZ01120000	15700AMZ01121000
Date of listing in the NHI reimbursement price	Feb 1983	Feb 1983
Date of initial marketing in Japan	Feb 1983	Feb 1983
Date of latest reexamination	Dec 1991	
Date of latest approval of indications	May 1985	

Caution : Use only as directed by a physician.

CONTRAINDICATIONS (MYONAL is contraindicated in the following patients.)
Patients with a history of hypersensitivity to any ingredients of MYONAL.

DESCRIPTION

1. Composition

Tablets 50 mg:

Each white, sugar-coated tablet contains 50 mg of eperisone hydrochloride.

It contains carnauba wax, carmellose, hydrated silicon dioxide, microcrystalline cellulose, titanium oxide, stearic acid, calcium stearate, sucrose, talc, precipitated calcium carbonate, corn starch, white shellac, hydroxypropylcellulose, pullulan, povidone and macrogol 6000 as inactive ingredients.

Granules 10%:

Each gram of white to yellowish white granules contains 100 mg of eperisone hydrochloride.

It contains carmellose, light anhydrous silicic acid, talc, corn starch, lactose hydrate, povidone, polyvinylacetal diethylaminoacetate and macrogol 6000 as inactive ingredients.

2. Product description

Brand name	Dosage form and identification code	Appearance			Description
		Face	Reverse	Lateral	
MYONAL Tablets 50mg	Sugar-coated tablets				White
	∈127	Diameter (mm) 7.5	Weight (mg) 162	Thickness (mm) 4.2	
MYONAL Granules 10%	Granules				White to yellowish white, coated granules having a faint characteristic odor

INDICATIONS

· Improvement of myotonic conditions caused by the following diseases:

Neck-shoulder-arm syndrome, scapulohumeral periarthritis and low back pain

· Spastic paralysis caused by the following diseases:

Cerebrovascular disorders, spastic spinal paralysis, cervical spondylosis, sequela of surgical trauma (including cerebrospinal tumor), sequela of trauma (spinal injury and head injury), amyotrophic lateral sclerosis, infantile cerebral palsy, spinocerebellar degeneration, spinal vascular disorders, subacute myelo-optico neuropathy (SMON) and other encephalomyelopathies

DOSAGE AND ADMINISTRATION

Tablets 50 mg:

The usual adult dosage for oral use is 3 tablets (150 mg of eperisone hydrochloride) daily in three divided doses after meals.

The dosage may be adjusted depending on the patient's age and symptoms.

Granules 10%:

The usual adult dosage for oral use is 1.5 g (150 mg of eperisone hydrochloride) daily in three divided doses after meals.

The dosage may be adjusted depending on the patient's age and symptoms.

PRECAUTIONS

1. Careful Administration (MYONAL should be administered with care in the following patients.)

(1) Patients with a history of drug hypersensitivity

(2) Patients with hepatic function disorder

[MYONAL may aggravate hepatic function.]

2. Important Precautions

Weakness, light-headedness, sleepiness or other symptoms may occur. In the event of such symptoms, the dosage should be reduced or treatment discontinued. Patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as operating machinery or driving a car.

3. Drug Interactions

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

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Methocarbamol	It has been reported that disturbance of visual accommodation occurred after the concomitant use of methocarbamol with tolperizone hydrochloride, an analogue compound.	Mechanism unknown

4. Adverse Reactions

Adverse reactions were reported in 416 of 12,315 patients (3.38%). (At the end of the reexamination period)

(1) Clinically significant adverse reactions (incidence unknown)

1) Shock and anaphylactoid reactions

Since shock and anaphylactoid reactions may occur, patients should be carefully observed. In the event of symptoms such as redness, itching, urticaria, edema of the face or other parts and dyspnea etc., treatment should be discontinued and appropriate measures taken.

2) **Oculo-muco-cutaneous syndrome (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell syndrome)**

Serious dermatopathy such as oculo-muco-cutaneous syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (Lyell syndrome) may occur. Patients should be carefully observed, treatment discontinued and appropriate measures taken, in the event of symptoms such as fever, erythema, blistering, itching, ocular congestion or stomatitis, etc.

(2) Other adverse reactions

	5% > ≥0.1%	<0.1%	Incidence unknown
Hepatic [note 1)]		Elevation of AST (GOT), ALT(GPT) and Al-P, etc.	
Renal [note 1)]		Proteinuria and Elevation of BUN, etc.	
Hematologic [note 1)]		Anemia	
Hypersensitivity [note 2)]	Rash	Pruritus	erythema exudativum multiforme
Psychoneurologic	Sleepiness, insomnia, headache and numbness in the extremities	Stiffness and tremor in the extremities	
Gastrointestinal	Nausea/vomiting, anorexia, stomach discomfort, abdominal pain, diarrhea, constipation and thirst	Stomatitis and feeling of enlarged abdomen	
Urinary		Urinary retention, urinary incontinence and feeling of residual urine	
General	Weakness, light-headedness and generalized fatigue	Muscle hypotonia and dizziness	
Others	Hot flushes	Diaphoresis and edema	

Note 1) Since these symptoms may occur, patients should be carefully observed. In the event of such abnormalities, treatment should be discontinued and appropriate measures taken.

Note 2) In the event of such symptoms, treatment should be discontinued.

5. 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.

6. Use during Pregnancy, Delivery or Lactation

(1) MYONAL should only be used in 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 MYONAL in pregnant women has not been established.]

(2) It is advisable to avoid the administration of MYONAL to nursing mothers. When MYONAL must be used, breast feeding should be discontinued during treatment.
[It has been reported that MYONAL is excreted in breast milk in an animal study (in rats).]

7. Pediatric Use

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

8. Precautions concerning Use

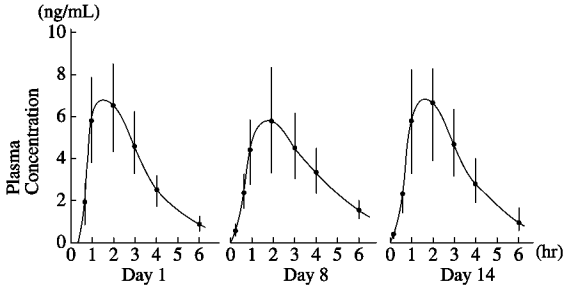
Caution in handing over drug (tablets)

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

Blood concentration

Eperisone hydrochloride was administered orally to 8 healthy adult male volunteers at a single dose of 150 mg/day [note)] for 14 consecutive days and the plasma concentration was determined at days 1, 8 and 14. The time to reach the peak plasma concentration (t_{max}) ranged from 1.6 to 1.9 hr, the peak plasma concentration (c_{max}) was 7.5 to 7.9 ng/mL, elimination half-life ($t_{1/2}$) was 1.6 to 1.8 hr, and the area under the plasma concentration-time curve (AUC) was 19.7 to 21.1 ng · hr/mL. The plasma concentration profiles of eperisone hydrochloride determined at days 8 and 14 did not significantly vary from those of the first day. [1)]



Plasma concentration of eperisone hydrochloride in the course of oral administration at a single dose of 150[note)] mg/day for 14 consecutive days (means ± S.E., n=8)

Note) A single dose of 150 mg is unapproved.

CLINICAL STUDIES

1. **Neck-shoulder-arm syndrome, scapulohumeral periarthritis and low back pain**
   In open labeled clinical trials and a double blind controlled clinical trial undertaken to determine the effects of MYONAL on myotonic symptoms associated with these diseases, an efficacy rate of 52.1% (234/449) was achieved. (When fairly effective responses are included, the efficacy rate was as high as 80.4%.) [2 - 4)]
2. **Spastic paralysis**
   In open labeled clinical trials and a double blind clinical trial, the usefulness of MYONAL has been established for spastic paralysis associated with diseases such as cerebrovascular disturbances, spastic spinal paralysis or cervical spondylosis. Improvement rates for rigidity and stiffness in patients with spastic paralysis were 42.3% (197/466) and 45.1% (174/386), respectively. [5 - 7)]

PHARMACOLOGY

1. **Skeletal muscle relaxation**
   (1) Inhibition of experimentally-induced muscle rigidity
   Eperisone hydrochloride suppresses intercollicular section-induced decerebrate rigidity (γ-rigidity) and ischemic decerebrate rigidity (α-rigidity) in rats dose-dependently. [8)]
   (2) Suppression of spinal reflexes
   In spinal cats, eperisone hydrochloride suppresses mono and poly-synaptic reflex potentials induced through spinal nerve efferent root stimulation to a similar degree. [8)]
   (3) Reduction of muscle spindle sensitivity via γ-motor neurons
   Eperisone hydrochloride suppresses the activity of afferent nerve fibers (Ia fibers) from human muscle spindles at 20 min after administration. Eperisone hydrochloride suppresses the spontaneous discharge of γ-motor neurons, but does not act directly on muscle spindles in animals. Accordingly, eperisone hydrochloride reduces muscle spindle sensitivity via the γ-motor neurons. [8, 9)]
2. **Vasodilatation and Augmentation of blood flow**
   (1) Vasodilatory action
   Eperisone hydrochloride dilates the blood vessels due to Ca^{++}-antagonistic action (in guinea pigs) on the vascular smooth muscle and muscular sympatholytic actions (in humans). [10, 11)]
   (2) Augmentation of blood flow
   Eperisone hydrochloride increases the volume of blood flow in skin, muscle, external and internal carotid arteries and vertebral arteries in humans, monkeys and dogs. [12 - 15)]
3. **Analgesic action and inhibition of the pain reflex in the spinal cord**
   When eperisone hydrochloride is perfused into the spinal cord of rats, a tail pinch-induced pain reflex is suppressed, but the reflex returns with the withdrawal of eperisone hydrochloride. This suggests that eperisone hydrochloride possesses an analgesic action at the spinal cord level. [16)]
4. **Facilitation of voluntary movement**
   When eperisone hydrochloride is used in the treatment of spastic paralysis in patients with cerebral apoplexy, it improves the cybex torque curve and electromyogram and facilitates voluntary movements, such as extension and flexion of the extremities, without reducing the muscular force. [17)]

PHYSICOCHEMISTRY

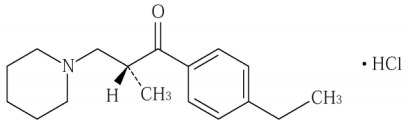
Nonproprietary name: Eperisone Hydrochloride (JAN)
Eperisone (INN)

Chemical name:
(2*RS*)-1-(4-Ethylphenyl)-2-methyl-3-piperidin-1-ylpropan-1-one monohydrochloride

Molecular formula: $C_{17}H_{25}NO \cdot HCl$

Molecular weight: 295.85

Structural formula:



and enantiomer

Description:
Eperisone hydrochloride occurs as a white, crystalline powder. It is freely soluble in water, in methanol and in acetic acid (100), soluble in ethanol (99.5).
A solution of eperisone hydrochloride in methanol (1 in 100) shows no optical rotation.

Melting point: About 167°C (decomposition)

PACKAGING

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

MYONAL Granules 10%: Cans of 100 g

REFERENCES

1) Tanaka S. et al.: Clin. Report, **16**, 6423, 1982.
2) Hanai K. et al.: Jap. J. Clin. Exp. Med., **60**, 2049, 1983.
3) Tawara T. et al.: Prog. Med., **3**, 1703, 1983.
4) Tsuyama N. et al.: Clin. Eval., **12**, 231, 1984.
5) Kuroiwa Y. et al.: *ibid*., **9**, 391, 1981.
6) Kobayashi I. et al.: Med. Consult. New Remed., **19**, 1493, 1982.
7) Tohgi H. et al.: *ibid*., **19**, 2073, 1982.
8) Tanaka K. et al.: Folia pharmacol. japon., **77**, 511, 1981.
9) Mano T. et al.: Brain Nerve, **33**, 237, 1981.
10) Fujioka M. et al.: J. Pharmacol. Exp. Ther., **235**, 757, 1985.
11) Iwase S. et al.: Electroenceph. Clin. Neurophysiol, **66**, S49, 1987.
12) Motomura K. et al.: Biomed. Thermography, **9**, 142, 1989.
13) Nanao K. et al.: 73th Folia pharmacol. japon. Abs. Kinki, 1988.
14) Sugimoto H. et al.: Clin. Report, **21**, 4882, 1987.
15) Mano T. et al.: 8th AOCN Satellite Symposium, 95, 1991.
16) Ishizuki M. et al.: J. Jpn. Orthop. Assoc., **63**, S1238, 1989.
17) Watanabe S. et al.: Jap. J. Clin. Exp. Med., **58**, 1610, 1981.

REQUEST FOR LITERATURE SHOULD BE MADE TO:

Safety Management Department
Fax: 03-3811-2710
Eisai Co., Ltd.

REQUEST FOR DRUG INFORMATION SHOULD BE MADE TO:

Customer Information Service
Free Dial: 0120-419-497
Eisai Co., Ltd.

Manufactured and marketed by:

Eisai Co., Ltd.
6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo, 112-8088