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Standard Commodity Classification No. of Japan
872329

- Gastric ulcer, duodenal ulcer and gastritis cure -

Methaphyllin[®] Combination Powder

Methaphyllin[®] Combination Tablet

Storage
METHAPHYLLIN should be stored at room temperature. Press-through packages of tablet should be protected from light and moisture after opening aluminum bag. See "PRECAUTIONS FOR HANDLING" section

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

	Combination Powder	Combination Tablet
Approval No.	22100AMX01558000	22100AMX00988000
Date of listing in the NHI reimbursement price	Sep 2009	Sep 2009
Date of initial marketing in Japan	Oct 1953	Oct 1954
Date of latest reevaluation	Jan 1986	

CONTRAINDICATIONS (METHAPHYLLIN is contraindicated in the following patients.)

1. Patients with glaucoma
[METHAPHYLLIN may increase intraocular pressure due to its anticholinergic action.]
2. Patients with urinary disorders due to prostatic hypertrophy
[METHAPHYLLIN may aggravate urinary disorders due to its anticholinergic action.]
3. Patients with severe heart disease
[METHAPHYLLIN may aggravate symptoms of heart disease.]
4. Patients with paralytic ileus
[METHAPHYLLIN may aggravate symptoms of paralytic ileus.]

DESCRIPTION

1. Composition

Combination Powder:

Each gram of greenish powder contains 30 mg of sodium copper chlorophyllin, 15 mg of propantheline bromide and 831.2 mg of magnesium silicate.




It also contains monosodium L-glutamate monohydrate, light anhydrous silicic acid, hydrogenated oil, tartaric acid, talc, partially hydrolyzed polyvinyl alcohol and flavor as inactive ingredients.

Combination Tablet:

Each greenish plain tablet contains 7.5 mg of sodium copper chlorophyllin, 3.75 mg of propantheline bromide and 160 mg of magnesium silicate.

It also contains carmellose, light anhydrous silicic acid, hydrogenated oil, tartaric acid, calcium stearate, talc, lactose hydrate and hydroxypropylcellulose as inactive ingredients.

2. Product description

Brand Name	Dosage form and identification code	Appearance			Description
		Face	Reverse	Lateral	
METHAPHYLLIN Combination Powder	Powder				Greenish, slightly specific fragrance
METHAPHYLLIN Combination Tablet	Plain Tablets				Greenish
	EISAI ML250	Diameter (mm) 9.1	Weight (mg) 250	Thickness (mm) 3.2	

INDICATIONS

Improvement of subjective and objective symptoms in the following diseases:

Gastric ulcer, duodenal ulcer, gastritis

DOSAGE AND ADMINISTRATION

Combination Powder:

The usual adult dosage for oral use is 1 g three to four times daily. The dosage may be adjusted depending on the patient's age and symptoms.

Combination Tablet:

The usual adult dosage for oral use is 4 tablets three to four times daily. The dosage may be adjusted depending on the patient's age and symptoms.

PRECAUTIONS

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

- (1) Patients with prostatic hypertrophy
[Urinary disorders may occur due to its anticholinergic action.]
- (2) Patients with hyperthyroidism
[METHAPHYLLIN may aggravate palpitations and

tachycardia accompanying hyperthyroidism.]

- (3) Patients with congestive heart failure
[METHAPHYLLIN may aggravate symptoms of congestive heart failure.]
- (4) Patients with arrhythmia
[METHAPHYLLIN may aggravate symptoms of arrhythmia.]
- (5) Patients with diarrhea
[METHAPHYLLIN may aggravate symptoms of diarrhea.]
- (6) Patients with ulcerative colitis
[Toxic megacolon colitis may occur.]
- (7) Patients exposed to high environmental temperature
[Fever may occur.]
- (8) Patients with severe renal function disorders
[Magnesium toxication may occur due to chronic administration.]
- (9) Elderly patients
[See “Use in the Elderly” section.]

2. Important Precautions

Since METHAPHYLLIN may produce visual accommodation disorder, drowsiness, etc., 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 (METHAPHYLLIN should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Tricyclic antidepressants Phenothiazine derivatives Antihistamines Anticholinergics	Potential of adverse reactions due to anticholinergic action may occur.	May potentiate anticholinergic action of propantheline bromide contained in METHAPHYLLIN.
Monoamine oxidase inhibitors	Potential of adverse reactions due to anticholinergic action may occur.	May inhibit the metabolism of METHAPHYLLIN and may potentiate its anticholinergic action of propantheline bromide contained in METHAPHYLLIN.
Tetracycline antimicrobial New quinolone antimicrobial Cefdinir Etidronate disodium	The blood concentration of the coadministered drug may be decreased and its effects may be diminished.	Magnesium silicate contained in METHAPHYLLIN and coadministered drug may form chelate complexes. Therefore the absorption of the coadministered drug may be inhibited.
Oral medications (Digoxin etc.)	The effects of the coadministered drug may be diminished.	Magnesium silicate contained in METHAPHYLLIN may adsorb oral medications or increase the pH of fluids in gastrointestinal tract. Hence the absorption or the excretion of coadministered drug may be influenced.

4. Adverse Reactions

Adverse reactions were reported in 108 of 1,135 patients (9.52%). (Total accumulation clinical trial)

	5%> ≥0.1%	<0.1%	Incidence unknown
Ophthalmic		Visual accommodation disorder	
Psychoneurologic	Dizziness	Headache, head heaviness and insomnia	Sleepiness
Gastrointestinal	Thirst, constipation, diarrhea, abdominal bloating and abdominal discomfort		Heartburn
Cardiovascular	Palpitations		
Hypersensitivity ^{note 1)}			Rash
Urinary	Urinary disorder		Renal calculus and urinary tract calculus ^{note 2)}
Metabolic disorder			Hypermagnesaemia ^{note 3)}
Others			Malaise, Facial hot flushes, feeling hot and hoarseness

Note 1) In the event of such symptoms, treatment should be discontinued.

Note 2) There are reports that these symptoms have occurred due to chronic and high dose administration of METHAPHYLLIN.

Note 3) There are reports that these symptoms have occurred due to chronic and high dose administration of magnesium silicate contained in METHAPHYLLIN. Therefore patient should be carefully observed. If any abnormality occurs, the dosage should be reduced or discontinued and appropriate measures taken.

5. Use in the Elderly

- (1) Since the elderly often develop adverse reactions such as urinary disorder, visual accommodation disorder, thirst or constipation, etc. due to the anticholinergic action of METHAPHYLLIN, they should take it under careful supervision.
- (2) Since renal function may be depressed in the elderly, care should be taken when administering as hypermagnesaemia may occur.

6. Use during Pregnancy, Delivery or Lactation

The safety of METHAPHYLLIN in pregnant women has not been established. (insufficient clinical experience).

7. Pediatric Use

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

8. Precautions concerning Use

Caution in handing over drug (Combination Tablet)

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.]

9. Others Precautions

Stools may appear dark greenish in color or their odor may be diminished after taking METHAPHYLLIN.

CLINICAL STUDIES

Clinical efficacy

The efficacy of METHAPHYLLIN for relief of abdominal pain and cure of gastrointestinal ulcer has been established in clinical studies to 1,135 patients with gastric or duodenal ulcer.¹⁻⁸⁾

PHARMACOLOGY

1. Antagonism to acetylcholine and spasmolytic effect on gastrointestinal tract

Propantheline bromide decreases the autonomic sensitivity, alleviates gastrointestinal tract spasms and relieves abdominal pain due to antagonism of acetylcholine at the parasympathetic nerve ending.⁹⁻¹¹⁾

2. Sustained antacid effect

Magnesium silicate neutralizes gastric acid and transforms to colloidal silicon dioxide which coats the gastrointestinal wall and causes a sustained antacid effect.

Additionally, suppression of gastric acid secretion by propantheline bromide prolongs the antacid effect.^{12), 13)}

3. Antipeptic effect and effect on proliferation of granulation

Sodium copper chlorophyllin suppresses the action of pepsin in the gastric juice, increasing the proliferation of granulation and promotes cure of ulcerative erosion.^{14), 15)}

4. Result of antiulcerative effect in experimental ulcerative models

Sodium copper chlorophyllin, propantheline bromide and magnesium silicate has been shown to suppress the ulceration of gastrointestinal tract in various experimental ulcerative rat model.

The combination of these components potentiated the antiulcerative effect synergistically.¹⁶⁻¹⁷⁾

PHYSICOCHEMISTRY

Nonproprietary name:

- 1) Sodium Copper Chlorophyllin
- 2) Propantheline Bromide
- 3) Magnesium Silicate

Chemical name:

- 1) Mixture of a and b type
 - (a type) copper complex salt of 1, 3, 5, 8-tetramethyl-4-ethyl-2-vinyl-9-oxo-10-carboxylphorb-7-propionic acid disodium
 - (b type) copper complex salt of 1, 5, 8-trimethyl-4-ethyl-2-vinyl-3-formyl-9-oxo-10-carboxylphorb-7-propionic acid disodium
- 2) *N*-Methyl-*N*, *N*-bis (1-methylethyl)-2-[(9*H*-xanthen-9-ylcarbonyl) oxy] ethylaminium bromide
- 3) magnesium silicate hydrate

Molecular formula and Molecular weight

- 1) (a type) $C_{34}H_{30}O_5N_4CuNa_2$ (684.16)
(b type) $C_{34}H_{28}O_6N_4CuNa_2$ (698.15)
- 2) $C_{23}H_{30}BrNO_3$ (448.39)
- 3) $Mg_2Si_3O_8 \cdot xH_2O$ (260.86+x18.02)

Description:

- 1) Sodium copper chlorophyllin occurs as blue-black to green-black powder. It is odorless and has a slightly specific fragrance.
It is very soluble in water and practically insoluble in ethanol (95) and in diethyl ether.
The pH of a solution of Sodium copper chlorophyllin (1 in 100) is between 9.5 and 11.0.
It is hygroscopic.
- 2) Propantheline bromide occurs as a white to yellowish white, crystalline powder. It is odorless and has a very bitter taste.
It is very soluble in water, in ethanol (95), in acetic acid (100) and in chloroform, soluble in acetic anhydride, and practically insoluble in diethyl ether.
The pH of a solution of Propantheline bromide (1 in 50) is between 5.0 and 6.0.
Melting point: about 161°C (with decomposition, after drying).
- 3) Magnesium silicate occurs as a white, fine powder. It is odorless and tasteless.
It is practically insoluble in water, in ethanol (95) and in diethyl ether.

PRECAUTIONS FOR HANDLING

1. Light may occur discoloration. Moisture may occur discoloration and may reduce the content of propantheline bromide.
Press-through packages of tablet should be protected from light and moisture after opening the aluminium bag.
2. Do not remove the powder from the packet or tablets from press-through packages at the time of dispensing.

PACKAGING

METHAPHYLLIN Combination Powder:

Boxes of 105g (1.0g packet×3×35), 1.26kg (1.0g packet×3×420)

METHAPHYLLIN Combination Tablet:

Boxes of 100 and 1,000 in press-through packages

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Safety Management Department

Fax: 03-3811-2710

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