PRODUCT MONOGRAPH

BONAMINE®

Meclizine Hydrochloride Tablets 25 mg, USP

Antiemetic Agent

McNeil Consumer Healthcare,
division of Johnson & Johnson Inc.
88 McNabb Street
Markham, Ontario L3R 5L2

Date of Revision: June 8, 2011

Control No. 142964

NAME OF DRUG

BONAMINE®
Meclizine Hydrochloride Tablets 25 mg, USP

THERAPEUTIC CLASSIFICATION

Antiemetic Agent

ACTION AND CLINICAL PHARMACOLOGY

Meclizine hydrochloride has antihistaminic and anticholinergic properties. The site and mechanism of its action in controlling vertigo arising from various conditions have not been clearly defined. Pharmacological studies conducted with other antihistamines show that the peripheral labyrinthine structures may be the site of action. The efficacy of meclizine hydrochloride in controlling the symptoms of motion sickness has been demonstrated in several fields studies, specifically in cases of airsickness and seasickness. Generally, it has been shown to be effective in over 80% of such cases, a single dose providing protection for approximately 24 hours with minimal side effects.

INDICATIONS

BONAMINE® (meclizine hydrochloride) is indicated for the prevention and relief of nausea, dizziness and vomiting associated with motion sickness. It is also indicated for the symptomatic management of radiation sickness, Meniere's syndrome, labyrinthitis and other vestibular disturbances.

CONTRAINDICATIONS

BONAMINE® (meclizine hydrochloride) is contraindicated in persons with known hypersensitivity to meclizine hydrochloride.

WARNINGS

Patients should be warned that BONAMINE® (meclizine hydrochloride) may occasionally cause drowsiness and that they should take the necessary precautions against driving or operating dangerous machinery when taking it.
Patients suffering from glaucoma or prostatic enlargement should take BONAMINE® (meclizine hydrochloride) only under the direction of a physician.

As with all antihistamines, meclizine may cause hyperexcitability in children.

PRECAUTIONS

Use in Pregnancy

Epidemiological studies with meclizine hydrochloride in women experiencing nausea and vomiting of pregnancy has revealed no evidence of a teratogenic effect attributable to the drug.

As with many other drugs of this class, certain teratogenic effects have been observed in the rat. In the rat, meclizine at doses of 25 to 50 times the human dose has shown certain fetal abnormalities. These abnormalities have not been observed in other experimental animals, including the monkey.

The use of BONAMINE® (meclizine hydrochloride) by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks.

Drug Interaction

There may be increased CNS depression when meclizine is administered concurrently with other CNS depressant, including barbiturates, alcohol, tranquilizers, and sedatives.

Monoaminooxidase (MAO) inhibitors may prolong and intensify the anticholinergic effects of meclizine.

ADVERSE REACTIONS

Drowsiness, dry mouth, fatigue, vomiting and on rare occasions, blurred vision have been reported with BONAMINE® (meclizine hydrocholoride) therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Signs and Symptoms: In adults, the usual signs of meclizine overdose are CNS depression with drowsiness, coma and convulsions. Hypotention may also occur, particularly in the elderly. In children, anticholinergic effects and CNS stimulation (hallucinations, seizures, trouble sleeping) are more likely to occur.

Treatment: There is no specific antidote for treatment of meclizine overdosage. Symptomatic and supportive treatment should be employed. If ingestion is recent (within one hour), induce emesis (syrup of ipecac is recommended; precautions against aspiration are required, especially in infants and children) or empty stomach by gastric lavage if patient has been unable to vomit within three hours of ingestion. Activated charcoal may also be used. Keep patient calm to minimize excitation. Vasopressors (norepinephrine or phenylephrine) may be used to correct hypotension. Physostigmine may be useful to counteract the CNS anticholinergic effects of meclizine. Do not use stimulants. If vasopressors are indicated do not use epinephrine, because it may lower blood pressure further. Diazepam I.V. may be given for treatment of seizures that do not respond to physostigmine.

DOSAGE AND ADMINISTRATION

The tablets should be swallowed whole, not chewed.

Adult Dosage

The recommended dose of BONAMINE® (meclizine hydrochloride) for specific indications is:

Motion sickness: A single dose of 25 to 50 mg of BONAMINE® affords protection against motion sickness for approximately 24 hours. The initial dose should be taken at least one hour prior to travelling in order to insure absorption of the drug, as retention of the medication is uncertain in individuals who have already developed motion sickness. Thereafter, the dose may be repeated every 24 hours as indicated for the duration of the journey.

Labyrinthine and vestibular disturbances: The optimal dosage is usually 25 to 100 mg daily in divided doses, depending on the clinical response.

Radiation sickness: 50 mg administered 2 to 12 hours prior to radiation treatment.

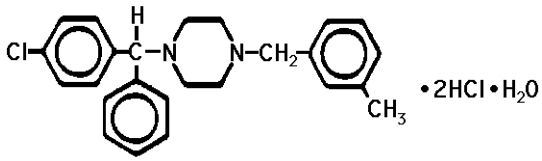
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name(s): Meclizine Hydrochloride, USP

Chemical Name(s): 1-(p-Chloro-α-phenylbenzyl)-4-(m-methylbenzyl)piperazine dihydrochloride monohydrate

Structural Formula: Meclizine hydrochloride.



Molecular Formula:
$C_{25}H_{27}ClN_2.2HCl.H_2O$

Molecular Weight: 481.89

Description: Meclizine hydrochloride USP is a white crystalline powder relatively insoluble in water (0.1g/100mL), and ether. Freely soluble in chloroform and pyridine.

Composition: BONAMINE® Tablets: Each yellow tablet contains: meclizine hydrochloride USP 25 mg. Also contains colloidal silicon dioxide, corn starch, D&C Yellow #10 aluminum lake, lactose anhydrous, magnesium stearate and microcystalline cellulose. Tartrazine-free.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15º and 25ºC. Protect from high humidity and heat.

AVAILABILITY OF DOSAGE FORMS

BONAMINE® Tablets: Each yellow tablet contains: meclizine hydrochloride USP 25 mg. Also contains colloidal silicon dioxide, corn starch, D&C Yellow #10 aluminum lake, lactose anhydrous, magnesium stearate, and microcystalline cellulose. Tartrazine-free. The product is supplied in an 8-count vial inside a carton and 3 x 8-count vials (24 tablets total) inside a carton.

PATIENT INFORMATION

BONAMINE®

Meclizine Hydrochloride Tablets 25 mg, USP

INDICATION

BONAMINE® (meclizine hydrochloride tablets) 25 mg, is indicated for the prevention and relief of motion sickness symptoms, such as nausea, vomiting and dizziness.

DIRECTIONS FOR USE

Adults and children over 12 years of age: Take one or two tablets, with water, at least one hour before travelling, for all-day protection against motion sickness. Swallow tablets whole; do not chew. The indicated dose may be taken once daily, if needed, during prolonged journeys.

WARNINGS

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health care professional before using this product.

Use BONAMINE® (meclizine hydrochloride) only upon doctor's advice if you have glaucoma, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland.

BONAMINE® (meclizine hydrochloride) may occasionally cause drowsiness. Take the necessary precautions agains driving or operating dangerous machinery. Alcohol, tranquilizers, sedatives and other drugs that have sedating effects may increase the drowsiness effect.

Important: Consult your doctor if symptoms persist beyond the end of the motion-sickness-causing journey.

CAUTION

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre, even if there are no symptoms.

INGREDIENT INFORMATION

BONAMINE® Tablets:

Medicinal Ingredient: each yellow tablet contains meclizine hydrochloride USP 25 mg.

Nonmedicinal Ingredients: colloidal silicon dioxide, corn starch, D&C Yellow #10 aluminum lake, lactose anhydrous, magnesium stearate and microcystalline cellulose. Tartrazine-free.

PHARMACOLOGY

Animal Studies

Early animal studies have demonstrated the antihistaminic properties of meclizine. In experiments with guinea pigs, a 16 mg/Kg oral dose protected 100% of the animals for up to 24 hours against ten times the minimum lethal dose of histamine administered intravenously, or against bronchospasms caused by exposure to 0.2% histamine aerosol. In common with other antihistamines, meclizine also possesses anticholinergic properties.

Human Studies

Several human clinical studies have demonstrated the efficacy of meclizine in controlling nausea and vomiting in postoperative situations, in pregnancy, as well as in treating vertigo of various etiologies.

In a placebo-controlled, comparative field trial involving over 400 young airmen with limited flying experience, a single dose of 25 mg meclizine, administered 24 hours before flights, afforded 61.1% protection against airsickness, which was significant ($p<0.01$) compared to placebo. While the comparator drugs, promethazine and scopolamine, afforded equivalent or better protection, each of these had to be administered 1 hour before flights to be effective, and were limited in their usefulness by side effects.

In a field study involving 12 susceptible service personnel aboard a U.S. Coast Guard cutter, daily single doses of 50 mg meclizine protected all twelve subjects against seasickness for the entire 8-day duration of the study.

In another, placebo-controlled, comparative field trial, involving over 1000 seamen receiving single daily doses of 50 mg meclizine, this drug regimen gave significant ($p<0.01$) protection against seasickness compared to placebo and was found to be more effective ($0.05<p<0.1$) than dimenhydrinate 100 mg t.i.d., buclizine 50 mg t.i.d., or promethazine 25 mg b.i.d. and significantly ($p<0.05$) more effective than 22 other drug regimens tested.

BONAMINE® Tablets versus BONAMINE® Chewable Tablets:
A single centre, randomized, single-dose, blinded, two-way crossover comparative bioavailability study of BONAMINE® Tablets (meclizine hydrochloride 25 mg tablets) versus BONAMINE® Chewable Tablets (meclizine hydrochloride 25 mg chewable tablets) was conducted in normal healthy adult male and female subjects (n = 48; 46 used in the pharmacokinetic analysis) aged 18 to 55 years under fasting conditions. It was concluded that the tablet was bioequivalent to the chewable tablet with respect to the evaluation criteria AUC_{0-t} and C_{max} and are therefore interchangeable. Results from this comparative bioavailability study are summarized below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Meclizine (1 x 25 mg) From measured data **uncorrected for potency** Geometric LS Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric LS Means	90% Confidence Interval
AUC_T (ng·h/mL)	326.406 372.872 (54.9)	290.299 335.647 (54.5)	112.44	106.59 - 118.61
AUC_∞ (ng·h/mL)	337.061 385.996 (55.6)	300.906 348.082 (55.1)	112.02	106.27 - 118.07
C_{max} (ng/mL)	54.706 61.547 (50.1)	48.091 54.270 (48.0)	113.75	105.51 - 122.64
T_{max}§ (h)	2.00 (1.00-6.00)	2.00 (1.00-6.00)		
$T_{½}$€ (h)	5.13 (42.7)	5.46 (40.1)		

* BONAMINE® Tablets (meclizine HCl 25 mg tablets); Manufacturer: McNeil Consumer Healthcare, division of Johnson & Johnson Inc., Canada
† BONAMINE® Tablets (meclizine HCl 25 mg chewable tablets); Manufacturer: McNeil Consumer Healthcare, division of Johnson & Johnson Inc., Canada, were marketed in Canada
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

TOXICOLOGY

Animal Toxicity Data

Acute toxicity (LD_{50}) following oral administration of meclizine was reported to be 1650 mg/Kg (range: 1330-2046 mg/Kg) in mice and 1500-3000 mg/Kg in rats.

Long-term toxicity studies (up to 6 months), conducted in rats and dogs at daily oral dosages of up to 350 mg/Kg or 50 mg/Kg respectively, revealed no untoward findings with respect to survival rates, blood chemistry, or tissue histology.

Teratology

In a study on pregnant rats, multiple daily oral doses of meclizine ranging from 25 to 250 mg/Kg, administered from days 7 through 15 of the pregnancy, were shown to produce significant numbers of skeletal and orofacial malformations in the offspring, with a frequency largely dependent on the administered dose.

However, the frequency of such malformations following single daily oral doses of meclizine ranging from 175 to 375 mg/Kg was only 0.84%, i.e., 3 malformed young out of 357 born. Furthermore, multiple daily oral doses of 250 mg/Kg meclizine, administered before the 11^{th} or after the 13^{th} days of pregnancy, produced no malformations.

Mutagenicity

In a study using the thymidine kinase locus in the mouse lymphoma (L5178Y) assay, with or without metabolic activation, meclizine showed no evidence of mutagenic activity.

Carcinogenicity

No long-term studies have been performed to evaluate the carcinogenic potential of meclizine.

Human Safety Experience

The relevance of the animal teratogenicity data to humans is highly questionable in view of the known species differences, especially with regard to the very relevant pharmacodynamic species difference in the effect of histamine, which acts as a vasoconstrictor in rodents while acting as a vasodilator in humans.

Be it as it may, results of several well controlled, prospective epidemiological studies obviated the early concern regarding the possible human teratogenicity of meclizine.
The total evidence, presented to and reviewed by the U.S. OTC Review Panel in this regard, involved epidemiological data on a total of over 50,000 pregnant women, 1,014 of whom used meclizine hydrochloride during the early stages of pregnancy. The data clearly indicated that the incidence of malformations was not statistically greater in the offspring of women in the meclizine group than in those in the control group.

In actual use, there were no serious side-effects reported that were attributable to meclizine. The most frequently reported adverse effects, such as nausea, weakness, dizziness or drowsiness, are difficult to distinguish from the symptoms of motion sickness itself. In any case, results of several double-blind, placebo-controlled, comparative studies show that the incidence of such side-effects associated with the use of meclizine is lower than that following the use of other antinauseant drugs, including dimenhydrinate.

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