METHYLERGONOVINE MALEATE- methylergonovine maleate tablet
American Health Packaging

Methylergonovine Maleate Tablets, USP
Rx Only
8441094/0918F

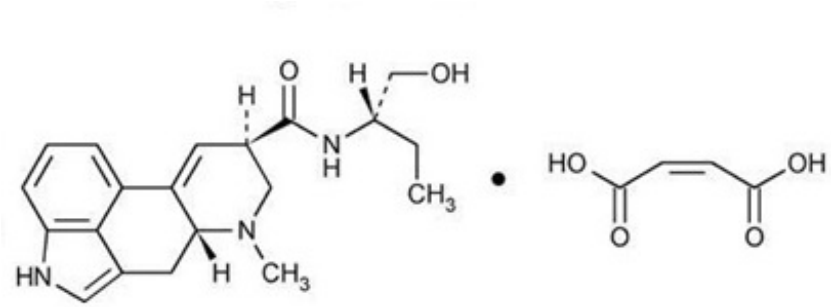
DESCRIPTION

Methylergonovine Maleate Tablets, USP is a semi-synthetic ergot alkaloid used for the prevention and control of postpartum hemorrhage.

Methylergonovine Maleate Tablets, USP is available in tablets for oral ingestion containing 0.2 mg methylergonovine maleate.

Tablets
Active ingredient: Methylergonovine maleate, USP, 0.2 mg.
Inactive ingredients: acacia, corn starch, gelatin, lactose monohydrate, methylparaben, microcrystalline cellulose, povidone, propylparaben, stearic acid, and tartaric acid.

Chemically, methylergonovine maleate is designated as ergoline-8-carboxamide, 9, 10-didehydro-N-[1-(hydroxymethyl) propyl]-6-methyl-, [8β(S)]-, (Z)-2-butenedioate (1:1) (salt). Its structural formula is:



$C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$ Mol Wt: 455.51

CLINICAL PHARMACOLOGY

Methylergonovine maleate acts directly on the smooth muscle of the uterus and increases the tone, rate, and amplitude of rhythmic contractions. Thus, it induces a rapid and sustained tetanic uterotonic effect which shortens the third stage of labor and reduces blood loss. The onset of action after I.V. administration is immediate; after I.M. administration, 2 to 5 minutes, and after oral administration, 5 to 10 minutes.

Pharmacokinetic studies following an I.V. injection have shown that methylergonovine is rapidly distributed from plasma to peripheral tissues within 2 to 3 minutes or less. The bioavailability after oral administration was reported to be about 60% with no accumulation after repeated doses. During delivery, with intramuscular injection, bioavailability increased to 78 %. Ergot alkaloids are mostly eliminated by hepatic metabolism and excretion, and the decrease in bioavailability following oral administration

is probably a result of first-pass metabolism in the liver.

Bioavailability studies conducted in fasting healthy female volunteers have shown that oral absorption of a 0.2 mg methylergonovine tablet was fairly rapid with a mean peak plasma concentration of 3243 ± 1308 pg/mL observed at 1.12 ± 0.82 hours. For a 0.2 mg intramuscular injection, a mean peak plasma concentration of 5918 ± 1952 pg/mL was observed at 0.41 ± 0.21 hours. The extent of absorption of the tablet, based upon methylergonovine plasma concentrations, was found to be equivalent to that of the I.M. solution given orally, and the extent of oral absorption of the I.M. solution was proportional to the dose following administration of 0.1, 0.2, and 0.4 mg. When given intramuscularly, the extent of absorption of methylergonovine maleate solution was about 25 % greater than the tablet. The volume of distribution (V_{dss}/F) of methylergonovine was calculated to be 56.1 ± 17.0 liters, and the plasma clearance (CLp/F) was calculated to be 14.4 ± 4.5 liters per hour. The plasma level decline was biphasic with a mean elimination half-life of 3.39 hours (range 1.5 to 12.7 hours). A delayed gastrointestinal absorption (T_{max} about 3 hours) of methylergonovine maleate tablet might be observed in postpartum women during continuous treatment with this oxytocic agent.

INDICATIONS AND USAGE

Following delivery of placenta, for routine management of uterine atony, hemorrhage and subinvolution of the uterus. For control of uterine hemorrhage in the second stage of labor following delivery of the anterior shoulder.

CONTRAINDICATIONS

Hypertension; toxemia; pregnancy; and hypersensitivity.

WARNINGS

General

This drug should not be administered I.V. routinely because of the possibility of inducing sudden hypertensive and cerebrovascular accidents. If I.V administration is considered essential as a lifesaving measure, methylergonovine maleate should be given slowly over a period of no less than 60 seconds with careful monitoring of blood pressure. Intra-arterial or periarterial injection should be strictly avoided.

Caution should be exercised in presence of impaired hepatic or renal function.

Breast-feeding

Mothers should not breast-feed during treatment with methylergonovine maleate. Milk secreted during this period should be discarded. Methylergonovine maleate may produce adverse effects in the breast-feeding infant. Methylergonovine maleate may also reduce the yield of breast milk. Mothers should wait at least 12 hours after administration of the last dose of methylergonovine maleate before initiating or resuming breast feeding.

Coronary artery disease

Patients with coronary artery disease or risk factors for coronary artery disease (e.g., smoking, obesity, diabetes, high cholesterol) may be more susceptible to developing

myocardial ischemia and infarction associated with methylergonovine-induced vasospasm.

Medication errors
Inadvertent administration of methylergonovine maleate to newborn infants has been reported. In these cases of inadvertent neonatal exposure, symptoms such as respiratory depression, convulsions, cyanosis and oliguria have been reported. Usual treatment is symptomatic. However, in severe cases, respiratory and cardiovascular support is required.

Methylergonovine maleate has been administered instead of vitamin K and Hepatitis B vaccine, medications which are routinely administered to the newborn. Due to the potential for accidental neonatal exposure, methylergonovine maleate injection should be stored separately from medications intended for neonatal administration.

PRECAUTIONS

General

Caution should be exercised in the presence of sepsis, obliterative vascular disease. Also use with caution during the second stage of labor. The necessity for manual removal of a retained placenta should occur only rarely with proper technique and adequate allowance of time for its spontaneous separation.

Drug Interactions

CYP 3A4 inhibitors (e.g., Macrolide Antibiotics and Protease Inhibitors)
There have been rare reports of serious adverse events in connection with the coadministration of certain ergot alkaloid drugs (e.g., dihydroergotamine and ergotamine) and potent CYP 3A4 inhibitors, resulting in vasospasm leading to cerebral ischemia and/or ischemia of the extremities. Although there have been no reports of such interactions with methylergonovine alone, potent CYP 3A4 inhibitors should not be coadministered with methylergonovine. Examples of some of the more potent CYP 3A4 inhibitors include macrolide antibiotics (e.g., erythromycin, troleandomycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (e.g., ritonavir, indinavir, nelfinavir, delavirdine) or azole antifungals (e.g., ketoconazole, itraconazole, voriconazole). Less potent CYP 3A4 inhibitors should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP 3A4 of other agents being considered for concomitant use with methylergonovine.

CYP3A4 inducers
Drugs (e.g. nevirapine, rifampicin) that are strong inducers of CYP3A4 are likely to decrease the pharmacological action of methylergonovine maleate.

Beta-blockers
Caution should be exercised when methylergonovine maleate is used concurrently with beta-blockers. Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.

Anesthetics

Anesthetics like halothan and methoxyfluran may reduce the oxytocic potency of methylergonovine maleate.

Glyceryl trinitrate and other antianginal drugs
Methylergonovine maleate produces vasoconstriction and can be expected to reduce the effect of glyceryl trinitrate and other antianginal drugs.

No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

Caution should be exercised when methylergonovine maleate is used concurrently with other vasoconstrictors, ergot alkaloids, or prostaglandins.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed in animals to evaluate carcinogenic potential. The effect of the drug on mutagenesis or fertility has not been determined.

Pregnancy

Category C: Animal reproductive studies have not been conducted with methylergonovine maleate. It is also not known whether methylergonovine maleate can cause fetal harm or can affect reproductive capacity. Use of methylergonovine maleate is contraindicated during pregnancy because of its uterotonic effects. (See INDICATIONS AND USAGE).

Labor and Delivery

The uterotonic effect of methylergonovine maleate is utilized after delivery to assist involution and decrease hemorrhage, shortening the third stage of labor.

Nursing Mothers

Mothers should not breast-feed during treatment with methylergonovine maleate and at least 12 hours after administration of the last dose. Milk secreted during this period should be discarded.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of methylergonovine maleate did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The most common adverse reaction is hypertension associated in several cases with

seizure and/or headache. Hypotension has also been reported. Abdominal pain (caused by uterine contractions), nausea and vomiting have occurred occasionally. Rarely observed reactions have included: acute myocardial infarction, transient chest pains, vasoconstriction, vasospasm, coronary arterial spasm, bradycardia, tachycardia, dyspnea, hematuria, thrombophlebitis, water intoxication, hallucinations, leg cramps, dizziness, tinnitus, nasal congestion, diarrhea, diaphoresis, palpitation, rash, and foul taste.

There have been rare isolated reports of anaphylaxis, without a proven causal relationship to the drug product.

Postmarketing Experience
The following adverse drug reactions have been derived from post-marketing experience with methylergonovine maleate via spontaneous case reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Nervous system disorders
Cerebrovascular accident, paraesthesia

Cardiac disorders
Ventricular fibrillation, ventricular tachycardia, angina pectoris, atrioventricular block

DRUG ABUSE AND DEPENDENCE

Methylergonovine maleate has not been associated with drug abuse or dependence of either a physical or psychological nature.

OVERDOSAGE

Symptoms of acute overdose may include: nausea, vomiting, oliquria, abdominal pain, numbness, tingling of the extremities, rise in blood pressure, in severe cases followed by hypotension, respiratory depression, hypothermia, convulsions, and coma.

Because reports of overdosage with methylergonovine maleate are infrequent, the lethal dose in humans has not been established. The oral LD_{50} (in mg/kg) for the mouse is 187, the rat 93, and the rabbit 4.5. Several cases of accidental methylergonovine maleate injection in newborn infants have been reported, and in such cases 0.2 mg represents an overdose of great magnitude. However, recovery occurred in all but one case following a period of respiratory depression, hypothermia, hypertonicity with jerking movements, and convulsions.

Also, several children 1 to 3 years of age have accidentally ingested up to 10 tablets (2 mg) with no apparent ill effects. A postpartum patient took 4 tablets at one time in error and reported paresthesias and clamminess as her only symptoms.

Treatment of acute overdosage is symptomatic and includes the usual procedures of:
1. removal of offending drug by inducing emesis, gastric lavage, catharsis, and supportive diuresis.
2. maintenance of adequate pulmonary ventilation, especially if convulsions or coma develop.
3. correction of hypotension with pressor drugs as needed.

4. control of convulsions with standard anticonvulsant agents.
5. control of peripheral vasospasm with warmth to the extremities if needed.

DOSAGE AND ADMINISTRATION

Orally
One tablet, 0.2 mg, 3 or 4 times daily in the puerperium for a maximum of 1 week.

HOW SUPPLIED

White, round, biconvex compressed tablets debossed with “G 786” on one side and plain on the other side.
Unit dose packages of 20 (2 x 10) NDC 60687-410-94

Store and Dispense
Tablets: Store at 20° to 25°C (68° to 77°F). [see USP Controlled Room Temperature]

FOR YOUR PROTECTION: Do not use if blister is torn or broken.

PACKAGING INFORMATION

American Health Packaging unit dose blisters (see How Supplied section) contain drug product from West-Ward Pharmaceuticals Corp.as follows:
(0.2 mg / 20 UD) NDC 60687-410-94 packaged from NDC 0054-0639

Distributed by:
American Health Packaging
Columbus, OH 43217

8441094/0918F

Package/Label Display Panel – Carton – 0.2 mg

NDC 60687- **410**-94

Methylergonovine Maleate Tablets, USP

0.2 mg

20 Tablets (2 x 10) **Rx Only**

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Keep this and all drugs out of reach of children.

FOR YOUR PROTECTION: Do not use if blister is torn or broken.

The drug product contained in this package is from
NDC # 0054-0639, West-Ward Pharmaceuticals Corp.

Distributed by:
American Health Packaging
Columbus, Ohio 43217

741094
0441094/0918OS

Package/Label Display Panel – Blister - 0.2 mg

Methylergonovine
Maleate
Tablet, USP

0.2 mg

METHYLERGONOVINE MALEATE

methylergonovine maleate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:60687-410(NDC:0054-0639)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METHYLERGONOVINE MALEATE (UNII: IR84JPZ1RK) (METHYLERGONOVINE - UNII:W53L6FE61V)	METHYLERGONOVINE MALEATE	0.2 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ACACIA (UNII: 5C5403N26O)	
STARCH, CORN (UNII: O8232NY3SJ)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
PROPYLPARABEN (UNII: Z8IX2SC1OH)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
TARTARIC ACID (UNII: W4888I119H)	

Product Characteristics			
Color	white	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	G;786
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:60687-410-94	20 in 1 BOX, UNIT-DOSE	11/01/2018	12/31/2024
1	NDC:60687-410-11	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210424	11/01/2018	12/31/2024

Labeler - American Health Packaging (929561009)

Establishment

Name	Address	ID/FEI	Business Operations
American Health Packaging		929561009	repack(60687-410)

Revised: 1/2024 American Health Packaging