

# **METHYLERGONOVINE MALEATE - methylergonovine maleate tablet** **Rising Pharma Holdings, Inc.**

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## **METHYLERGONOVINE MALEATE Tablets, USP** **Rx only**

### **DESCRIPTION**

Methylergonovine maleate is a semi-synthetic ergot alkaloid used for the prevention and control of postpartum hemorrhage.

Methylergonovine maleate is available in tablets for oral ingestion containing 0.2 mg methylergonovine maleate.

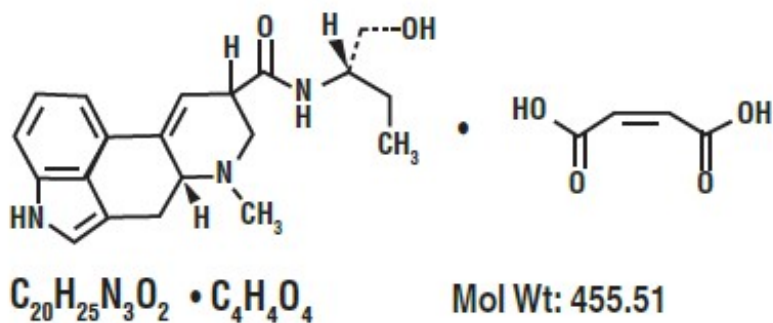
### **Tablets**

*Active ingredient:* Methylergonovine maleate, USP, 0.2 mg.

*Inactive ingredients:* acacia, corn starch, gelatin, lactose monohydrate, methyl paraben, microcrystalline cellulose, povidone, propyl paraben, stearic acid, and tartaric acid.

Chemically, methylergonovine maleate is designated as ergoline-8-carboxamide, 9, 10-didehydro-*N*-[1-(hydroxymethyl) propyl]-6-methyl-, [8 $\beta$ (*S*)]-, (*Z*)-2-butenedioate (1:1) (salt).

Its structural formula is:



### **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, 2-5 minutes, and after oral administration, 5-10 minutes.

Pharmacokinetic studies following an I.V. injection have shown that methylergonovine is rapidly distributed from plasma to peripheral tissues within 2-3 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  $3243 \pm 1308$  pg/mL observed at  $1.12 \pm 0.82$  hours. For a 0.2 mg intramuscular injection, a mean peak plasma concentration of  $5918 \pm 1952$  pg/mL was observed at  $0.41 \pm 0.21$  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 ( $V_{d_{SS}}/F$ ) of methylergonovine was calculated to be  $56.1 \pm 17.0$  liters, and the plasma clearance ( $CL_p/F$ ) was calculated to be  $14.4 \pm 4.5$  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 new born 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 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**

#### ***CYP3A4 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 CYP3A4 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**

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 & 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.<sup>1</sup>

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

**To report SUSPECTED ADVERSE EVENTS, contact Rising Pharma Holdings, Inc. at 1-844-874-7464 or FDA at 1-800-FDA-1088 or <http://www.fda.gov/> for voluntary reporting of adverse reactions.**

## **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, oliguria, 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<sub>50</sub>(in mg/kg) for the mouse is 187, the rat 93, and the rabbit 4.5. Several cases of accidental methylergonovine maleate injection in new born 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 1-3 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 to off-white, round shape, biconvex compressed tablets debossed with "C" on one side and "2" on the other side.

Available in bottles of 7, 12, 28 and 100 tablets.

Bottles of 7	NDC 16571-735-17
Bottles of 12	NDC 16571-735-21
Bottles of 28	NDC 16571-735-28
Bottles of 100	NDC 16571-735-01

## **STORE AND DISPENSE**

Tablets: Store at 20 - 25° C (68 - 77° F) [see USP Controlled Room Temperature]; in tight, light-resistant container.

### **Distributed by:**

Rising Pharma Holdings, Inc.  
East Brunswick, NJ 08816

Made in India

Code: TS/DRUGS/19/1993

Revised: 08/2020

PIR73501-00

**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**

**Methylergonovine maleate tablets, USP**

**Container Labels**

**Rising®**

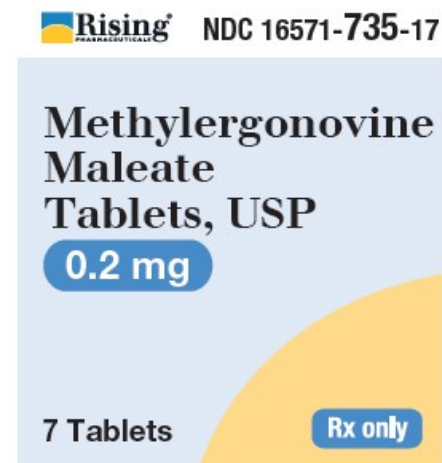
**NDC 16571-735-17**

**Methylergonovine  
Maleate  
Tablets, USP**

**0.2 mg**

**7 tablets**

**Rx Only**



Usual Dosage: See package insert.

Store at 20 - 25°C (68 - 77°F) [See  
USP Controlled Room  
Temperature].

Dispense in a tight, light-resistant  
container

Keep this and all drugs out of the  
reach of children.

**Distributed by:**

Rising Pharma Holdings, Inc.  
East Brunswick, NJ 08816

**Made in India**

Code: TS/DRUGS/19/1993

Revised: 08/2020

LR73517-00



P1426870

**Rising®**

**NDC 16571-735-21**

**Methylergonovine  
Maleate  
Tablets, USP**

**0.2 mg**

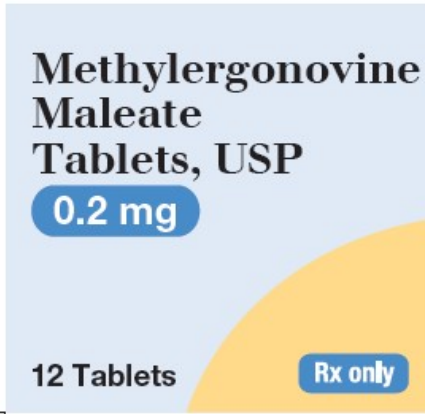
**12 tablets**

**Rx Only**

**Rising** NDC 16571-735-21

Usual Dosage: See package insert.

**Distributed by:**  
Rising Pharma Holdings, Inc.  
East Brunswick, NJ 08816



Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

**Made in India**  
Code: TS/DRUGS/19/1993  
Revised: 08/2020  
LR73521-00

Dispense in a tight, light-resistant container

Keep this and all drugs out of the reach of children.

P1426871



**Rising**

**NDC 16571-735-28**

**Methylergonovine Maleate Tablets, USP**

**0.2 mg**

**28 tablets**

**Rx Only**

**Rising** NDC 16571-735-28

Usual Dosage: See package insert.

**Distributed by:**  
Rising Pharma Holdings, Inc.  
East Brunswick, NJ 08816



Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

**Made in India**  
Code: TS/DRUGS/19/1993  
Revised: 08/2020  
LR73528-00

Dispense in a tight, light-resistant container

Keep this and all drugs out of the reach of children.

P1426872



**Rising**

**NDC 16571-735-01**

**Methylergonovine Maleate Tablets, USP**

**0.2 mg**

**100 tablets**

**Rx Only**



**Rising** NDC 16571-735-01

Usual Dosage: See package insert.

**Distributed by:**  
Rising Pharma Holdings, Inc.  
East Brunswick, NJ 08816



# Methylergonovine Maleate Tablets, USP

0.2 mg

Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

**Made in India**  
Code: TS/DRUGS/19/1993  
Revised: 08/2020  
LR73501-00

Dispense in a tight, light-resistant container

P1426873

100 Tablets

Rx only

Keep this and all drugs out of the reach of children.

## METHYLERGONOVINE MALEATE

methylergonovine maleate tablet

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:16571-735
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>METHYLERGONOVINE MALEATE</b> (UNII: IR84JPZ1RK) (METHYLERGONOVINE - UNII:W53L6FE61V)	METHYLERGONOVINE MALEATE	0.2 mg

### Inactive Ingredients

Ingredient Name	Strength
<b>ACACIA</b> (UNII: 5C5403N26O)	
<b>STARCH, CORN</b> (UNII: O8232NY3SJ)	
<b>GELATIN, UNSPECIFIED</b> (UNII: 2G86QN327L)	
<b>LACTOSE MONOHYDRATE</b> (UNII: EWQ57Q8I5X)	
<b>METHYLPARABEN</b> (UNII: A2I8C7HI9T)	
<b>MICROCRYSTALLINE CELLULOSE</b> (UNII: OP1R32D61U)	
<b>POVIDONE K30</b> (UNII: U725QWY32X)	
<b>STEARIC ACID</b> (UNII: 4ELV7Z65AP)	
<b>TARTARIC ACID</b> (UNII: W4888I119H)	
<b>PROPYLPARABEN</b> (UNII: Z8IX2SC1OH)	

### Product Characteristics

<b>Color</b>	WHITE (off-white)	<b>Score</b>	no score
<b>Shape</b>	ROUND (biconvex)	<b>Size</b>	6mm
<b>Flavor</b>		<b>Imprint Code</b>	C;2
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:16571-735-17	7 in 1 BOTTLE; Type 0: Not a Combination Product	01/15/2021	
2	NDC:16571-735-21	12 in 1 BOTTLE; Type 0: Not a Combination Product	01/15/2021	
3	NDC:16571-735-28	28 in 1 BOTTLE; Type 0: Not a Combination Product	01/15/2021	
4	NDC:16571-735-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	01/15/2021	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211919	01/15/2021	

**Labeler** - Rising Pharma Holdings, Inc. (835513529)

## Establishment

Name	Address	ID/FEI	Business Operations
Aurobindo Pharma Limited		918917642	ANALYSIS(16571-735) , LABEL(16571-735) , MANUFACTURE(16571-735) , PACK(16571-735)

Revised: 11/2021

Rising Pharma Holdings, Inc.