Physician's Package Insert

PAPAVERINE TEVA INJECTION

Solution for I.M. or I.V Injection

Composition
Each ampoule of 2 ml contains

Active Ingredient
Papaverine hydrochloride 40 mg

Other Ingredients
Water for injections, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment).

Mechanism of Action
The most characteristic effect of papaverine is relaxation of the tonus of smooth muscle of all types, especially when the muscle has been spasmodically contracted. This relaxation effect is expressed in the vascular system, bronchial musculature and in the gastrointestinal, biliary and urinary tracts.

The antispasmodic effect of papaverine is direct and unrelated to muscle innervation.

Papaverine mildly stimulates respiration in certain circumstances by acting on carotid and aortic body chemoreceptors.

Papaverine may increase cerebral blood flow and at the same time decrease cerebral vascular resistance in normal subjects; oxygen consumption is unaltered. These effects may explain the reported benefits of the drug in cerebral vascular encephalopathy.

Indications
As an antispasmodic in the following conditions:

- Visceral spasm, e.g., gastrointestinal colic, biliary and urinary tract spasms.
- Peripheral vascular disease in which there is a vasospastic element.
- Vascular spasm associated with acute myocardial infarction, angina pectoris, peripheral and pulmonary embolism.

Contraindications
Known hypersensitivity to the preparation.

Complete AV heart block. When conduction is depressed, the drug may produce transient ectopic rhythms of ventricular origin, either premature beats or paroxysmal tachycardia.

Papaverine Teva Injection is contraindicated in patients who have conditions that might predispose them to priapism such as sickle cell anaemia, multiple myeloma or leukaemia.

Warnings
Large doses can depress AV and intraventricular conduction, and thereby produce serious arrhythmias. When conduction is depressed, papaverine may produce transient ectopic rhythms of ventricular origin, premature beats or paroxysmal tachycardia (see Contraindications). Elderly patients should undertake an ECG before being prescribed this product to eliminate the existence of cardiac conduction disorders.
In patients with acute coronary thrombosis, the occurrence of ventricular cardiac arrhythmias is serious and requires measures designed to decrease myocardial irritability.

Hepatic toxicity: Chronic hepatitis, as evidenced by elevations of hepatic enzymes and bilirubin have been reported during use of papaverine. Most of the affected patients were also consuming alcohol and a causal relationship to papaverine has not been proven. Routine monitoring of hepatic function during papaverine therapy is not required. However, patients with a history of alcohol abuse or liver disease should be followed more closely with liver function tests obtained before initiating treatment and at 6-monthly intervals.

Use in Pregnancy
Safety for use in pregnancy has not been established. Therefore, this drug should be used only when clearly needed, and when the anticipated benefits outweigh the unknown potential hazards to the fetus.

Use in Lactation
It is not known whether this drug is excreted in human milk. Safety for use in nursing mothers has not been established.

Use in Pediatrics
Safety for use in children has not been established.

Use in Patients with Impairment of Hepatic Function
Papaverine Teva Injection should be used with caution in patients with pre-existing hepatic impairment because of the potential for exacerbation (see Hepatic Toxicity). If signs or symptoms of exacerbated hepatic impairment occur during papaverine therapy, the drug should be discontinued.

Adverse Reactions
General discomfort, nausea, abdominal distress, anorexia, sweating, malaise, vertigo, drowsiness, excessive sedation, skin rash, constipation or diarrhea, increase in depth of respiration, slight increase in blood pressure.

Symptoms/signs resulting from vasodilation include headache, flushing, a sensation of heat in the pelvis, dizziness, photopsia, tachycardia, hypotension and syncope.

Liver function abnormalities, hepatitis, probably related to an immune mechanism, has been reported infrequently. Rarely, this has progressed to cirrhosis.

Other
Vasovagal reactions, cardiac events, allergic reactions, urticaria, impaired ejaculation, death (one report).

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

Precautions
The medication should be discontinued if hepatic hypersensitivity with gastrointestinal symptoms, jaundice or eosinophilia becomes evident or if liver function test values become altered. (see Warnings).
Use with caution in patients with glaucoma. Patients who experience excessive sedation, drowsiness or vertigo upon treatment with this drug, should be cautioned against engaging in potentially-hazardous activities requiring mental alertness, such as driving a car or operating machinery. Patients should be advised to take care when getting up from a lying or sitting position or when climbing stairs because of the possibility of postural hypotension.

**Drug Interactions**

**Papaverine/ Levodopa:** The antiparkinsonism effectiveness of levodopa may be decreased by concomitant administration of papaverine, due to possible blockade of dopamine receptors. Several Parkinsonian patients maintained on levodopa have developed worsening of their Parkinsonism following papaverine administration. The therapeutic response to levodopa returned 5 to 10 days after the papaverine was stopped. The use of papaverine in these patients should be avoided.

**Papaverine/ Diazoxide:** I.V. injection should not be administered within 6 hours of the administration of papaverine-like compounds. Potentiation of antihypertensive effects may occur.

**Papaverine/ CNS Depressants/Morphine:** The effects of papaverine may be slightly potentiated by CNS depressants and a synergism may result from combination with morphine.

**Effect on Laboratory Tests**
Liver function test results (serum ALT, AST and bilirubin concentrations as well as eosinophil count) may be altered during intravenous papaverine therapy.

**Drug Abuse and Dependence**
Drug dependence resulting from the abuse of many of the selective depressants, including papaverine hydrochloride, has been reported.

**Dosage and Administration**

*Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.*

Papaverine is intended for I.M. or I.V. administration in doses of 30-120 mg. Intravenous use should be reserved for cases where an immediate effect is desired. Administration should be slow (1-2 minutes).

**Overdosage**

*Manifestations*
The symptoms of toxicity from papaverine hydrochloride often result from vasomotor instability and include nausea, vomiting, weakness, central nervous system depression, nystagmus, diplopia, diaphoresis, flushing, dizziness, and sinus tachycardia. In large overdoses papaverine is a potent inhibitor of cellular respiration and a weak calcium antagonist. Following an oral overdose of 15 g, metabolic acidosis with hyperventilation, hyperglycemia and hypokalemia have been reported. No information on toxic serum concentrations is available.

Following intravenous overdosing in animals, seizures, tachyarrhythmias, and ventricular fibrillation have been reported. The oral median lethal dose in rats is 360 mg/kg

*Treatment*
In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient. Protect the patient’s airway and support ventilation and perfusion. Meticulously monitor vital signs, blood gases, blood chemistry values, and other variables.
If convulsions occur, consider diazepam, phenytoin, or phenobarbital. If the seizures are refractory, general anesthesia with thiopental or halothane and paralysis with a neuromuscular blocking agent may be necessary.

For hypotension, consider intravenous fluids, elevation of the legs, and an inotropic vasopressor, such as dopamine or levarterenol. Theoretically, calcium gluconate may be helpful in treating some of the toxic cardiovascular effects of papaverine; monitor the ECG and plasma calcium concentrations.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of papaverine hydrochloride.

**Pharmaceutical Precautions**

Papaverine Teva Injection should not be added to Lactated Ringer's Injection, since precipitation will result.

**Storage**

Store below 25°C.
Do not freeze.

**Drug Registration No.:** 027 68 22028

**Manufacturer and License Holder**

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