SUMMARY OF PRODUCT CHARACTERISTICS

Papaverine Teva Injection 40 mg/2 ml
Solution for I.V. or I.M. Injection

1. NAME OF THE MEDICINAL PRODUCT

Papaverine Teva Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampule of 2 ml solution for injection contains 40 mg of papaverine hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Method of administration
Intramuscular or intravenous route.

Posology
Papaverine should be administered by or under the immediate supervision of a physician.
Papaverine administration should be discontinued if any sign or symptom of liver tenderness occurs in the treated patient.
ECG monitoring should be performed before and during parenteral treatment.

Adults:
From 30 to 120 mg.
Administration should be slow (1-2 minutes).
Intravenous use should be reserved for cases where an immediate effect is desired.

4.3 Contraindications

- Hypersensitivity to papaverine or any of the other ingredients mentioned in section 6.1.
- Intravenous injection: contraindicated in patients with complete atrioventricular block.
- Severe heart failure.
- Recent myocardial infarction.
- Recent heart attack.
- Heart rhythm disorders (bradycardia).
- In case of intracranial hypertension.
- Hepatic disease.

4.4 Special warnings and precautions for use

- A too rapid intravenous injection may lead to arrhythmias and fatal apnea.
- Due to the risk of heart rhythm disorders, caution should be exercised in cases of cardiac conduction disorders or unstable cardiovascular diseases.
- Administration of papaverine should be discontinued if symptoms of hepatotoxicity occur.
- Liver and blood tests should be regularly monitored in patients on chronic papaverine treatment.
- Papaverine should be administered with caution to patients with decreased gastrointestinal motility as they are more exposed to digestive disorders.
- Intravenous injection is not recommended for children under 15 years of age.

This medicine contains less than 1 mmol sodium (23 mg) per ampule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Papaverine reduces the therapeutic effect of levodopa (antiparkinsonian agent).
If papaverine is given while being treated with calcium antagonists, it is possible that they may increase the effect of papaverine.
Due to its weak antiarrhythmic properties, papaverine may increase the effects of similar medicinal products such as hypotensive agents.
Nicotine can reduce or even abolish the vasodilator effects of papaverine.
The effects of papaverine may be slightly potentiated by concomitant use of central nervous system depressants and a synergistic effect may be expected when combined with morphine.

4.6 Fertility, pregnancy and lactation

Fertility
There are no adequate studies in humans or animals regarding the effects of papaverine on fertility or reproduction.

Pregnancy
There are no data on the use of papaverine in pregnant women. Animal studies are not sufficient to assess the reproductive toxicity (see section 5.3).
Papaverine is not recommended during pregnancy or for women who may be pregnant and do not use contraception.

Breast-feeding
It is not known whether papaverine or its metabolites pass into breast milk. A risk to the breastfed infant cannot be excluded.
A decision must be made whether or not to discontinue breastfeeding or to discontinue treatment with papaverine, taking into account the benefit of breastfeeding for the infant with regard to the benefit of treatment for the woman.

4.7 Effects on ability to drive and use machines
Caution should be exercised with respect to driving and using machines as papaverine hydrochloride administration may cause drowsiness and dizziness.

4.8 Undesirable effects
The adverse effects of papaverine described in the literature are listed below and classified by system organ class and frequency. The frequencies are defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table: Known side effects		
System organ class	**Undesirable effects**	**Frequency**
Nervous system disorders (Autonomic Nervous System)	increased depth of breathing, depression, dizziness, lightheadedness, headache, drowsiness, sedation, lassitude, alertness disorder, malaise, weakness and lethargy.	Rare
Cardiac disorders	increased heart rate, arrhythmias (too rapid injection or injection of too high doses), atrioventricular block, tachycardia	Rare
Vascular disorders	hypotension or increased blood pressure	Rare
Gastrointestinal disorders*	constipation, nausea, diarrhea, abdominal distress and anorexia, vomiting	Rare
Skin and subcutaneous disorders	pruritus, rash,	Rare
Hepatobiliary disorders	Hepatotoxicity: Hepatitis and increased hepatic enzymes (alkaline phosphatase, SGOT) suggesting hepatotoxicity.	Not known
General disorders and administration site conditions	Hypersensitivity reactions	Very rare
	General discomfort, redness in the face, sweating, dry mouth and throat	Rare
	Thrombosis at the injection site.	Not known

* subjects with bowel movement disorders are more easily exposed to digestive disorders.

Reporting of suspected adverse reactions
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
https://sideeffects.health.gov.il

4.9 Overdose

Symptoms
Overdose may cause vasomotor instability with nausea, vomiting, weakness, central nervous system depression, flushing, lightheadedness, stroke, heart rhythm disorders and tachycardia. Acute overdose is expressed in hypotension and cardiorespiratory depression.

Treatment
At the first signs of overdose, treatment should be discontinued and the treating physician should be notified who will decide whether hospitalization is required.

In case of overdose, symptomatic treatment consists of supporting patient ventilation and blood circulation.
Vital signs (blood gas and cardiac conduction) should be monitored.
In case of seizures, parenteral administration of diazepam, phenytoin or phenobarbital will be started.
In case of refractory seizures, thiopental and halothane may be used to induce general anesthesia and a neuromuscular blocking agent may be used to cause paralysis.
To treat hypotension, administer intravenous fluids and, if necessary, sympathomimetic agents (norepinephrine).
For the treatment of heart disorders, intravenous administration of calcium gluconate together with ECG monitoring may be helpful.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Smooth muscle antispasmodic, including for the gastrointestinal and urogenital system.
ATC code: A03AD01.

Papaverine is a direct-acting and non-specific smooth muscle relaxant causing an effect on the blood vessels (vasodilator action) and other smooth muscle systems. Papaverine can also depress conduction in the heart muscle and prolong the diastolic period.
The cerebral blood flow is increased in most cases, and this effect has a short duration. The peripheral vasodilator effect is of variable intensity and probably depends on the development stage of artery and arteriole wall sclerosis, and therefore is probably inversely proportional to the severity of the vascular pathology. Papaverine is effective in the symptomatic treatment or prevention of spasms.
Papaverine blocks, to a certain extent, the flow of Ca++ ions across the cell membrane, which explains the anti-tachyarrhythmic activity. The intensity of this blockage may vary from one vascular site to another as well as from one individual to another.

It is clear that the wide range of pharmacological activities makes papaverine useful in a great variety of vessel and/or visceral conditions. The effect is evident in most cases, with a short duration, and non-curative.

5.2 Pharmacokinetic properties
After injection, papaverine hydrochloride is rapidly distributed in the organism.
The half-life time is 90-130 minutes and the apparent volume of distribution is 0.99-1.52 L/kg.
The substance is highly bound to plasma proteins (87%). After intravenous administration of a 1 mg/kg dose, a blood level of 1 mg/L is reached in 5 minutes.

Metabolism
Ninety percent of papaverine hydrochloride is metabolized in the liver in a few hours. The initial step of metabolism is demethylation to 6-hydroxypapaverine or 4-hydroxypapaverine and, in turn, their phenolic group is affected by the glucurono- or sulfoconjugation. It should be noted that 4-hydroxypapaverine also has a clinically significant phosphodiesterase inhibitory activity.

Elimination
Elimination is carried out by the renal route as unmetabolized papaverine (less than 1% is found unchanged in the urine) and as metabolites (more than 50%). The rest is eliminated by the bile.

5.3 Preclinical safety data
The treatment of pregnant mice and rats with papaverine did not increase the frequency of congenital malformations.
Other reproductive and fetal development toxicity data from standard animal studies are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment), Water for Injections.

6.2 Incompatibilities
Do not add the papaverine solution to a lactated Ringer's solution as it may form a precipitate.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C.
Do not freeze.

6.5 Nature and contents of container
Carton box containing 10 amber glass ampoules.

Each ampoule contains 2 ml solution.

6.6 Special precautions for disposal and handling

Before administration, Papaverine Teva Injection should be drawn out according to the rules of good clinical practice, in the most aseptic manner possible, using a sterile syringe, immediately after opening the ampule. The drawn out drug solution should then be administered immediately.

The solution should be visually inspected prior to administration for any particulate matter.
Do not use the solution if the liquid is not clear. Discard ampules containing visible particles.

This solution does not contain any antimicrobial preservative and is therefore for single use, which is not likely to prevent microorganism growth.
Any unused medicinal product must not be stored for later use.
Any unused product or waste material should be disposed of in accordance with the current regulations.

In general, there is a risk of irritation or necrosis at the injection site in case of too rapid administration or if too much volume is injected.

7. LICENCE HOLDER AND MANUFACTURER

TEVA ISRAEL LTD
124 Dvora HaNevi'a St., Tel Aviv 6944020 Israel

8. REGISTRATION NUMBER

027.68.22028

This leaflet was revised in January 2022 according to Ministry of Health guidelines.