

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Papaverine Hydrochloride

120 mg/10mL

Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Papaverine Hydrochloride Injection is supplied in ampoules containing 30 mg or 120 mg of papaverine hydrochloride BP.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

DBL™ Papaverine Hydrochloride Injection is a sterile, clear, colourless to pale-yellow solution. The pH of the injection ranges between 3.0 and 5.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL™ Papaverine Hydrochloride Injection is indicated for the treatment of erectile dysfunction.

4.2 Dose and method of administration

DBL™ Papaverine Hydrochloride Injection should only be prescribed, and treatment should be supervised, by prescribers having expertise in the management of erectile dysfunction using a range of treatment modalities.

The 300 mg/10 mL ampoule of DBL™ Papaverine Hydrochloride Injection must only be used for treatment of a single patient, on one occasion only.

The use of DBL™ Papaverine Hydrochloride Injection in combination with other agents, including phentolamine and alprostadil is not recommended (see section 4.4).

DBL™ Papaverine Hydrochloride Injection should be administered by intracavernosal injection.

Before initiation of treatment with DBL™ Papaverine Hydrochloride Injection, patients should be carefully assessed by a specialist practitioner in erectile dysfunction with

appropriate training in the use of this drug. The dose should be titrated carefully according to individual need. The first injection of DBL™ Papaverine Hydrochloride Injection must be done by medically trained personnel. After proper training and instruction, DBL™ Papaverine Hydrochloride Injection may be injected at home. If self-administration is planned, the specialist should make an assessment of the patient's (or as appropriate, the partner's) skill and competence with the procedure. While on self-injection treatment, it is recommended that the patient visit the specialist's office at periodic intervals. At that time, the efficacy and safety of the therapy should be assessed, and the dose of DBL™ Papaverine Hydrochloride Injection should be adjusted, if needed.

Dosage

The lowest effective dose should be determined for each patient. In general most patients respond to doses in the range of 2.5 to 60 mg of papaverine hydrochloride.

A starting dose of 15 mg is recommended for patients with erectile dysfunction due to most causes. Patients with psychogenic erectile dysfunction are likely to respond to lower doses, while those with vasculogenic erectile dysfunction are likely to require higher doses. Patients who do not respond to a dose of 60 mg should be changed to alternative therapy.

A starting dose of 5 mg is recommended for men with erectile dysfunction due to spinal cord injury.

Erection usually occurs within 10 minutes of injection of the drug and may persist for one to several hours. Tolerance to papaverine hydrochloride may occur during long-term use and may require an increase in dosage.

The dose should be reduced if erections persist for longer than four hours. Early studies using doses of up to 80 mg papaverine hydrochloride resulted in high proportion patients requiring assisted detumescence.

Dosage adjustment should be made carefully, based on the degree and duration of tumescence achieved with the previous dose.

General procedure for injection

Ampoules of DBL™ Papaverine Hydrochloride Injection are intended for single use only and should be discarded after use. The 300 mg/10 mL ampoule is for use in one patient only, on one occasion only.

Intracavernosal papaverine hydrochloride may be self-administered by patients, but only after careful training in the technique to reduce the incidence of inadvertent subcutaneous administration, ecchymosis and urethral injury.

The patient should be instructed to use a new syringe and needle for each injection and in the appropriate disposal of the syringe and the needle. Needle breakage, with a portion of the needle remaining in the penis, has been reported and in some cases, required hospitalisation and surgical removal. The patient should be cautioned against using bent needles, to inject DBL™ Papaverine Hydrochloride Injection or attempting to straighten a bent needle prior to injecting.

Following is the general procedure for injection.

1. Prior to administration, visually inspect DBL™ Papaverine Hydrochloride Injection for particulate matter and discolouration.
2. Using a needle, withdraw the required dosage. A 13 mm, 27 to 30 gauge needle is recommended.
3. Stretch the penis out across the thigh, with the foreskin retracted in uncircumcised men. Clean the site with an alcohol swab. Do not inject along the midline. Do not inject through any of the superficial veins that are clearly visible under the skin. Inject over one to two minutes into either of the two corpora cavernosa. Inject at 90 degrees to the skin; the needle should be inserted up to the needle hub to ensure that the corpus is injected.
Note: Subsequent injections should be alternated between the two cavernosa. The injection site should be varied from the base of the penis to just proximal to the glans avoiding the midline and any veins. Injections should not be made into the underside of the penis.
4. After injecting, remove the needle and apply pressure to the injection site with the alcohol swab until any bleeding stops. The entire length of the corpus cavernosum should be squeezed firmly to distribute medication, followed by the same procedure on the other side. The penis should then be pinched transversely in several places to distribute medication to both ends of the corpus cavernosum. This procedure should result in an erection that is adequate for intercourse.

4.3 Contraindications

DBL™ Papaverine Hydrochloride Injection is contraindicated in patients with complete atrioventricular block.

DBL™ Papaverine Hydrochloride Injection is contraindicated in patients who have conditions that might predispose them to priapism such as sickle cell anaemia, multiple myeloma or leukaemia. Patients with pre-existing penile fibrosis should not be accepted into intracavernosal self-injection therapy. DBL™ Papaverine Hydrochloride Injection should not be used in patients with anatomical deformation of the penis, such as angulation, cavernosal fibrosis or Peyronie's disease.

DBL™ Papaverine Hydrochloride Injection should not be used in men for whom sexual activity is inadvisable or contraindicated.

DBL™ Papaverine Hydrochloride Injection should not be used in patients with penile implants.

4.4 Special warnings and precautions for use

Priapism

Intracavernosal injection of DBL™ Papaverine Hydrochloride Injection has caused priapism. **Treatment of priapism should not be delayed. Patients should be instructed to seek urgent medical attention if an erection lasts for more than four hours.** Priapism has been managed by aspiration of cavernosal blood and/or intracavernosal injection of small doses of an α -adrenergic agonist. Parenteral administration of high doses may cause cardiac arrhythmia and fatal apnoea; a slow rate of intravenous administration is recommended (over a 1 to 2 minute period) to avoid serious adverse effects.

Penile Fibrosis

Patients should be carefully assessed for pre-existing penile fibrosis before initiation of treatment with intracavernosal Papaverine Hydrochloride Injection. If pre-existing penile fibrosis is found, the patient should not be accepted into intracavernosal self-injection therapy. This assessment should be made during pharmacologically-induced erection. At regular visits, the physician must examine the penis carefully, preferably in the erect state, for potential development of fibrotic changes. If there are signs of fibrotic complications, treatment with DBL™ Papaverine Hydrochloride Injection must be stopped immediately. Development of penile fibrosis appears to be related to the injection volume being in excess of 1 mL. During self-injection therapy, the patient must be instructed to report to the physician any unusual new adverse effects such as increased or new penile pain, penile bending and/or nodule formation in the penile shaft.

Other Precautions

Caution is also advised in the presence of cardiac conduction disorders or unstable cardiovascular disease. Extreme care should be taken when conduction is depressed since the drug may produce transient ectopic rhythms of ventricular origin, either premature beats or paroxysmal tachycardia. Elderly patients should undertake an ECG before being prescribed this product to eliminate the existence of cardiac conduction disorders.

Patients on anticoagulants such as warfarin or heparin may have an increased propensity for bleeding after the intracavernosal injection.

The injection of papaverine hydrochloride can induce a small amount of bleeding at the site of injection. In patients infected with blood-borne diseases, this could increase the transmission of such diseases to the partner.

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.

Combination Therapy

The physical compatibility and stability of papaverine hydrochloride with alprostadil and/or phentolamine in mixed preparations has not been established. Co-administration of papaverine hydrochloride with alprostadil and/or phentolamine was associated with an increased risk of adverse events including dizziness and syncope in evaluated trials. The safety and efficacy of combination therapy with papaverine hydrochloride and phentolamine and/or alprostadil has not been established.

The use of papaverine hydrochloride in combination with oral agents for erectile dysfunction has not been established.

Use in Hepatically Impaired Patients

DBL™ Papaverine Hydrochloride Injection should be used with caution in patients with pre-existing hepatic impairment (liver disease) because of the potential for exacerbation (see below). If signs or symptoms of exacerbated hepatic impairment occur during papaverine hydrochloride therapy, the drug should be discontinued.

Liver Function Abnormalities

Elevations of hepatic enzymes and bilirubin have been reported during use of papaverine hydrochloride. Most of the affected patients were also consuming alcohol and a causal relationship to papaverine hydrochloride has not been proven. Routine monitoring of hepatic function during papaverine hydrochloride 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.

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 hydrochloride therapy.

4.5 Interaction with other medicines and other forms of interaction

The effects of papaverine hydrochloride may be slightly potentiated by CNS depressants and a synergism may result from combination with morphine.

Papaverine hydrochloride may interfere with the therapeutic effects of levodopa in patients with Parkinson's disease when the drugs are administered concomitantly. Several Parkinsonian patients maintained on levodopa have developed worsening of their Parkinsonism following papaverine hydrochloride administration. The therapeutic response to levodopa returned 5 to 10 days after the papaverine was stopped. The use of papaverine hydrochloride in these patients should be avoided.

Patients on anticoagulants such as warfarin or heparin may have an increased propensity for bleeding after the intracavernosal injection.

Ioxaglate can form a paste-like precipitate with papaverine hydrochloride, and this could have serious consequences should precipitation occur in the penis.

4.6 Fertility, pregnancy and lactation

Fertility

There are no adequate human or animal studies addressing the effect of papaverine hydrochloride on fertility or reproductive performance.

Pregnancy

Category B3

DBL™ Papaverine Hydrochloride Injection is not intended for use by women.

In animal studies, a single 140 mg/kg subcutaneous dose of papaverine hydrochloride to mice on gestation day 9 (timed to coincide with neural tube closure) caused increased foetal mortality and retardation, spinal cord kinking and dilation of the fourth brain ventricle. Neither neural anomaly was observed in control foetuses. Neural tube defects were also observed in explanted mouse and chick embryos exposed to 50-75 microgram/mL papaverine

hydrochloride during neurulation *in vitro*. The relevance of these animal findings to humans is currently unknown.

There are no formal studies of papaverine hydrochloride in pregnant women.

Lactation

DBL™ Papaverine hydrochloride Injection is not intended for use by women.

It is not known whether papaverine hydrochloride is excreted in breast milk. Because many drugs are excreted in breast milk, caution should be exercised when papaverine hydrochloride is administered to a nursing woman.

4.7 Effects on ability to drive and use machinery

No data available.

4.8 Undesirable effects

Intracavernosal injection of papaverine hydrochloride may cause mild discomfort in the penis during injection, ecchymosis at the injection site, urethral bleeding, paraesthesiae of the glans, difficulty in reaching orgasm and ejaculation, and priapism. **Treatment of priapism should not be delayed. Patients should be instructed to seek urgent medical attention if an erection lasts for more than four hours.**

Following is a listing of local and systemic adverse effects from clinical studies and case reports in which papaverine hydrochloride was used.

Local Adverse Events

- Prolonged erection/priapism
- Penile fibrosis, manifested as subcutaneous nodules, plaques, cavernosal fibrosis, scarring, deformity, curvature (Peyronie's disease) and calcification
- Pain/ discomfort/ burning sensations during the injection
- Injection site bruising/ haematoma
- Injection site blister/ ulcer
- Penile/ foreskin oedema
- Loss of penile sensation
- Misplaced injections, sometimes leading to urethral bleeding
- Pain during erection
- Infection/ cavernositis/ pyogenic granuloma
- Thrombophlebitis/ lymphangitis
- Intracorporal needle breakage
- Fixed drug eruption
- Penile fracture

Systemic Adverse Events

- Liver function abnormalities

- Symptoms/ signs resulting from vasodilation including headache, flushing, a sensation of heat in the pelvis, dizziness, photopsia, tachycardia, hypotension and syncope.
- Vasovagal reactions
- Cardiac events
- Allergic reactions, urticaria
- Impaired ejaculation
- Death (one report)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Symptoms

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 hydrochloride is a potent inhibitor of cellular respiration and a weak calcium antagonist. Following an oral overdose of 15 g, metabolic acidosis with hyperventilation, hyperglycaemia, and hypokalemia have been reported. No information on toxic serum concentrations is available.

Overdose of papaverine hydrochloride via the intracavernosal route is likely to result in priapism. **Patients should be instructed to seek urgent medical attention if an erection lasts for more than four hours.**

Patients should be instructed to seek medical help immediately if they have self-administered an overdose of papaverine hydrochloride.

Treatment

In managing overdosage, a physician must consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics.

The patient's airway must be protected, and ventilation and perfusion supported. Vital signs, blood gases, blood chemistry values and other variables need to be monitored.

In the event of convulsions, administration of diazepam or phenytoin needs to be considered. If seizures are refractory, general anaesthesia with thiopentone or halothane and paralysis with a neuromuscular blocking agent may be necessary.

For hypotension, intravenous fluids, elevation of legs and administration of an inotropic vasopressor, such as dopamine, need to be considered. Theoretically, calcium gluconate may be helpful in treating some of the toxic cardiovascular effects of papaverine hydrochloride; the ECG and plasma calcium concentrations need to be monitored.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Papaverine hydrochloride is the hydrochloride of an alkaloid obtained from opium or prepared synthetically. It belongs to the benzyloisoquinoline group of alkaloids. The principal therapeutic action of papaverine hydrochloride is its relaxant effect on smooth muscles, which leads to penile erection. It may induce erections by arteriolar relaxation, increased blood flow and volume due to relaxation of the sinusoidal wall of the corpora cavernosa and subsequent compression of venous channels between the sinusoids and the tunica albuginea.

The spasmolytic effect of papaverine hydrochloride is most pronounced on the vascular system, including coronary, cerebral, pulmonary and peripheral vasodilation; it also relaxes the bronchial, gastrointestinal, biliary and urinary tract smooth muscles. Papaverine hydrochloride has also been reported to have direct cardiac inotropic effects, leading to increased myocardial oxygen consumption, which can outstrip the effect of increased coronary blood flow if hypotension is also present. It can depress myocardial excitability, prolong the refractory period and depress myocardial conduction. In the presence of depressed conduction due to other causes (eg AV block), papaverine hydrochloride may produce transient ventricular arrhythmias. Papaverine hydrochloride can mildly stimulate respiration via action on the carotid and aortic body chemoreceptors.

Papaverine hydrochloride has minimal Central Nervous System (CNS) actions, although large doses may have a depressant effect in some patients. The drug also exhibits weak calcium-channel blocking activity at high doses. Papaverine hydrochloride has been reported to have antiviral activity against respiratory syncytial virus, cytomegalovirus, measles and HIV. It may inhibit mitochondrial oxidative reactions, which can lead to severe lactic acidosis following large doses, especially overdose.

5.2 Pharmacokinetic properties

The extent and time-course of papaverine hydrochloride absorption have not been documented. In theory, systemic absorption following intracavernosal injection would initially be rapid, until the local effect of papaverine hydrochloride led to occlusion of the venous outflow from the penis. Absorption would then be slow, but would pick up again as detumescence occurred and the sequestered blood was returned to the systemic circulation.

Papaverine hydrochloride has a relatively short plasma half-life (1-2 hours) and is rapidly metabolised by the liver and excreted in the urine, chiefly as the glucuronide conjugates of phenolic metabolites. The drug is excreted in the urine in an inactive form. Approximately 90% of the drug is bound to plasma proteins. After intracavernosal injection, the peak plasma concentration is several times lower than after extracavernosal injection.

5.3 Preclinical safety data

Genotoxicity

In an Ames test, papaverine hydrochloride was weakly mutagenic to the TA100 but not the TA98 strain of *Salmonella typhimurium*, only in the presence of metabolic activation.

Carcinogenicity

No long-term animal studies on the carcinogenic potential of papaverine hydrochloride have been performed.

Reproductive and developmental toxicity

There are no adequate human or animal studies addressing the effect of papaverine hydrochloride on fertility or reproductive performance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

6.2 Incompatibilities

A precipitate results when DBL™ Papaverine Hydrochloride Injection is added to lactated Ringer's Injection.

6.3 Shelf life

36 months

6.4 Special precautions for storage

DBL™ Papaverine Hydrochloride Injection should be stored below 25°C and protected from light.

6.5 Nature and contents of container

DBL™ Papaverine Hydrochloride Injection is supplied in clear glass ampoules in the following presentations and pack sizes:

DBL™ Papaverine Hydrochloride Injection 120 mg/10 mL 5 x 10 mL ampoules

DBL™ Papaverine Hydrochloride Injection 30 mg/1 mL 5 x 1 mL ampoules (supplied under Section 29)

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pfizer New Zealand Limited

P O Box 3998

Auckland, New Zealand, 1140

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

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Summary table of changes

Section changed	Summary of new information
All	Reformat to MedSafe Data Sheet guidance