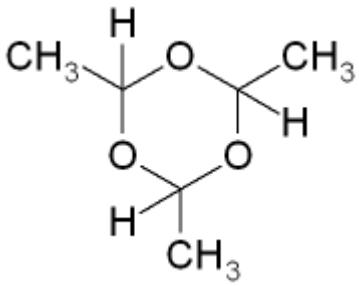
PRODUCT INFORMATION

PARALDEHYDE INJECTION BP

NAME OF THE MEDICINE

Name:	Paraldehyde
The molecular formula:	$(C_2H_4O)_3$
Chemical Name:	2,4,6-trimethyl-1,3,5-trioxane
Molecular weight :	132.2
CAS registry number :	123-63-7

Structural Formula:



DESCRIPTION

Paraldehyde Injection BP is a sterile liquid. Each vial contains 5 mL of paraldehyde and 500 micrograms of hydroquinone as an antioxidant. It is a colourless or pale yellow transparent liquid, with a strong odour and disagreeable burning taste. Paraldehyde is soluble 1 in 10 of water, but is only soluble 1 in 17 in boiling water. It is miscible with alcohol, chloroform, ether and volatile oils. Paraldehyde solidifies to form a crystalline mass at low temperatures, but can be liquefied by warming. Paraldehyde is a cyclic trimer of acetaldehyde.

PHARMACOLOGY

Pharmacodynamics

Paraldehyde has sedative and hypnotic actions. It is believed to depress many levels of the central nervous system (CNS), including the ascending reticular activating system to cause an imbalance between inhibitory and facilitatory mechanisms. Doses of 4 to 10 mL administered intramuscularly (IM) have produced sleep within 5 to 15 minutes which lasted about 8 hours in patients with normal liver function. In sub-hypnotic doses, paraldehyde has anticonvulsant actions, although the dose margin between the anticonvulsant and hypnotic effects is small. At sub-anaesthetic doses, it is not an analgesic and may produce excitement or delirium in the presence of pain.

Pharmacokinetics

Absorption

Paraldehyde is rapidly absorbed from intramuscular injection sites. Maximum serum levels, which may range from 34 to 150 micrograms/mL are reached within 20 to 60 minutes of intramuscular injection of 0.25 mL/kg. The drug diffuses into the cerebrospinal fluid (CSF) and also crosses the placental barrier. Maximum paraldehyde concentrations have been reached in the CSF, 30 to 60 minutes after intramuscular administration of the drug.

Distribution

Although tissue distribution of paraldehyde has not been extensively studied, it is known that the concentration of the drug in CSF is approximately 25 to 30% lower than that in the blood.

Metabolism

It appears that about 80 to 90% of the dose is metabolised in the liver to acetaldehyde, which is oxidised by aldehyde dehydrogenase to acetic acid, then further metabolised to carbon dioxide and water.

Excretion
A significant proportion of the drug is excreted unchanged through the lungs (giving a characteristic odour to the breath) and only small amounts are excreted unchanged in the urine. The biological half life of paraldehyde is approximately 3.5 to 9.5 hours with an average of 7.5 hours in patients with normal liver function.

INDICATIONS
Paraldehyde has been used as a sedative and hypnotic in a variety of clinical situations, although it has been largely replaced by safer and/ or more effective agents. It may also be used in the treatment of convulsive episodes arising from tetanus, status epilepticus and poisoning by convulsive drugs, when other agents are inappropriate or ineffective. Paraldehyde may be effective in reducing the anxiety associated with withdrawal from drugs such as narcotics or barbiturates, as well as in the management of acute agitation or delirium tremens due to alcohol withdrawal. Paraldehyde is only recommended for use in these conditions when other treatments are ineffective or deemed inappropriate.

CONTRAINDICATIONS
Paraldehyde is contraindicated in patients hypersensitive to the drug.

Paraldehyde is contraindicated in patients with severe hepatic insufficiency.

Paraldehyde should not be used for obstetric anaesthesia, as the drug diffuses across the placenta and has been known to cause respiratory depression in neonates.

Paraldehyde Injection BP is contraindicated in patients with bronchopulmonary disease, as unmetabolised paraldehyde (11 to 28%) is excreted via exhalation.

PRECAUTIONS
Use only freshly opened vials. Paraldehyde Injection BP must not be used if the container has been opened as it decomposes on storage. The administration of partly decomposed paraldehyde is dangerous as it may cause metabolic acidosis. Deaths from corrosive poisoning have been reported following the use of decomposed paraldehyde. It must not be used if it has a brownish colour or a sharp penetrating odour of acetic acid.

Due to the solvent action of paraldehyde, plastic syringes must not be used. Contact between paraldehyde and rubber should be avoided.

Avoid contact with the skin, eyes and clothing.

Prolonged use of paraldehyde may lead to dependence of the barbiturate-alcohol type, especially in alcoholics. Prolonged use may also produce tolerance and physical and/or psychological dependence on the drug. Sudden withdrawal of paraldehyde from physically dependent persons may cause delirium tremens and hallucinations. In dependent persons, the drug should be withdrawn slowly.

Toxic hepatitis, nephrosis, and metabolic acidosis have been reported following prolonged use of paraldehyde (see **ADVERSE EFFECTS).**

Paraldehyde Injection BP should not be administered subcutaneously because it is irritating to tissues.

Avoid intramuscular injection near nerve trunks as this may cause severe and permanent nerve damage (see **ADVERSE EFFECTS).**

Intravenous administration is extremely hazardous since it may cause pulmonary oedema and haemorrhage, hypotension and cardiac dilatation, and circulatory collapse. Thrombophlebitis is also associated with intravenous administration. Paraldehyde should be used cautiously, if at all, in patients with cardiovascular disease, asthma or other bronchopulmonary disease.

Impaired hepatic function may result in unpredictable rates of paraldehyde metabolism and so it should be administered with caution to patients with hepatic dysfunction. Close observation should be employed to detect signs of paraldehyde toxicity. Paraldehyde is contraindicated in severe hepatic insufficiency.

Use as a hypnotic or sedative should be short term only. Patients should be warned that the hypnotic effect occurs very rapidly. Paraldehyde causes drowsiness. Hence, patients receiving Paraldehyde Injection BP should not drive a motor vehicle or operate machinery.

This product contains low levels of crotonaldehyde which is known to be genotoxic and carcinogenic. Due to the content of crotonaldehyde, the recommended maximum life –time dose of Paraldehyde that any individual should receive is 30 mL

Use in pregnancy
Category D

Paraldehyde readily diffuses across the placenta and has been known to cause respiratory depression in neonates (see **CONTRAINDICATIONS**). Therefore the use of Paraldehyde Injection BP in pregnancy is contraindicated. Pregnancy should be excluded before commencing therapy.

Use in Lactation
It is not known whether paraldehyde crosses into breast milk although problems in humans have not been documented. Nevertheless because many drugs are excreted in human milk and because of the potential for serious adverse reactions due to paraldehyde in breastfed infants, a decision should be made either to discontinue breastfeeding or the drug, taking into account the importance of the drug to the mother.

INTERACTION WITH OTHER MEDICINES

Concomitant administration of paraldehyde with other CNS depressants such as barbiturates or alcohol should be avoided due to possible potentiation of CNS depression.

Animal studies indicate that disulfiram slows the metabolism of paraldehyde via inhibition of acetaldehyde dehydrogenase resulting in an increase in blood concentrations of paraldehyde and acetaldehyde. Therefore concomitant administration of paraldehyde and disulfiram should be avoided.

ADVERSE EFFECTS

Intramuscular administration of Paraldehyde Injection BP is extremely painful and has produced sterile skin abscesses, sloughing of skin, fat necrosis, and muscular irritation. Severe and permanent nerve damage has occurred when paraldehyde was injected intramuscularly too close to nerve trunks; care must be taken when administered by the intramuscular route.

Intravenous administration of Paraldehyde Injection BP is not recommended as it has caused pulmonary oedema, pulmonary haemorrhage, dilatation of the right side of the heart, circulatory collapse, thrombophlebitis, respiratory distress and cyanosis.

Paraldehyde Injection BP may cause skin rashes. Other side effects, such as dizziness, muscle cramps, trembling and unusual sweating have been reported.

Toxic hepatitis and nephrosis have been reported following prolonged use of paraldehyde. Metabolic acidosis has also occurred following overdosage of Paraldehyde Injection BP and has been associated with nausea, muscular tremor, severe epigastric cramps, mental confusion, agitation, pseudoketosis, hyperacetaldehydemia. Prolonged use may also produce tolerance and physical and/or psychological dependence on the drug.

DOSAGE AND ADMINISTRATION

Paraldehyde Injection BP may be administered intramuscularly undiluted by deep injection into the buttocks taking care to avoid the vicinity of the nerve trunks. Not more than 5 mL should be administered per injection site. The usual doses are as follows:

Indication	Adult Dose	Children's Dose
Hypnotic	10mL IM	0.3mL/kg/daily IM
Sedative	5mL IM	0.15mL/kg/daily IM
Convulsions (*e.g.,* tetanus)	5 to 10mL IM	Not recommended
Convulsions from poisons	5 to 10mL IM	Not recommended
Status epilepticus	5 to 10mL IM	0.1 to 0.15mL/kg/dose dose IM every 4 to 8 hours
Alcohol withdrawal	5mL IM every 4 to 6 hours for 24 hours then every 6 hours. Maximum of 30mL IM on first day and 20mL/day IM thereafter.	

For further information regarding recommended life-time intake, please refer to the PRECAUTIONS section.

Use in one patient on one occasion only and discard. Contains no antimicrobial preservative. Refer to **STORAGE** section.

Incompatibilities

Due to its solvent action, paraldehyde is incompatible with many plastics and rubber. The use of plastic syringes for storage or administration of paraldehyde and contact with rubber should therefore be avoided. Needles with plastic hubs may be used with Paraldehyde Injection BP. The use of polypropylene syringes with rubber tipped plastic plungers, or glass syringes with natural rubber tipped plastic plungers is acceptable only for the immediate administration or measurement of paraldehyde doses. It is recommended that all glass syringes should be used for the injection of paraldehyde.

OVERDOSAGE

Paraldehyde overdosage results in short and troubled, rapid breathing. Other characteristics include cloudy urine, decreased urination, a slow heartbeat and general weakness. This may lead to coma, severe hypotension, respiratory depression, pulmonary oedema and cardiac failure. Paraldehyde induced coma may last for several hours because it is slowly metabolised. Paraldehyde overdosage is distinguished from other CNS depressants by the odour of the drug on the breath. Metabolic acidosis with increased anion gap may also occur. Renal function may be impaired and may result in azotaemia, oliguria and albuminuria. Nephrosis, fatty changes in the kidneys or liver and/or toxic hepatitis may also occur.

Fatalities are uncommon, but when they occur they are usually caused by respiratory failure. A few fatalities have been attributed to pulmonary oedema and right sided heart failure or metabolic acidosis.

Treatment

Treatment should be supportive and symptomatic and should include re-establishment of adequate respiratory exchange by maintenance of an adequate airway, control of respiration and oxygen administration.

Metabolic acidosis may be corrected by intravenous (IV) administration of sodium bicarbonate or sodium lactate.

Body temperature should be maintained and circulation supported, with intravenous fluids or vasopressors, if necessary.

PRESENTATION AND STORAGE CONDITIONS

Paraldehyde Injection BP is presented as a 5mL glass vial in a pack of 5 vials.

AUST R 160612

Phebra product code- INJ153

Store below 25°C. Protect from light. Do not refrigerate. Use promptly after opening. Do not use if solution has a brownish colour or a sharp penetrating odour of acetic acid. Paraldehyde solidifies to form a crystalline mass at temperatures around 12°C. Warm gently if crystallised.

NAME AND ADDRESS OF THE SPONSOR

Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.
ABN 77 695 661 635

In New Zealand, Paraldehyde Injection BP is distributed by:
AFT Pharmaceuticals Ltd, PO Box 33-203 Takapuna, Auckland.

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods: 31 August 2009
Date of most recent amendment: 03 June 2015