SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Chloral Hydrate 500mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of Chloral Hydrate Oral Solution contains 500 mg of chloral hydrate.

Excipients with known effect

Each 5 ml of Chloral Hydrate Oral Solution contains 1655 mg of liquid glucose, 6.3 mg of sodium benzoate, 3525 mg of glycerol and 18.39 mg of propylene glycol. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution.

Clear colourless solution with a fruity odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

Chloral Hydrate Oral Solution is indicated for the short-term treatment (maximum 2 weeks) of severe insomnia which is interfering with normal daily life and where other therapies (behavioural and pharmacologic) have failed. Chloral Hydrate Oral Solution should be used as an adjunct to non-pharmacological therapies.

Children and adolescents aged 2 years and above:

Chloral Hydrate Oral Solution is indicated for the short-term treatment (maximum 2 weeks) of severe insomnia in children and adolescents with suspected or definite neurodevelopmental disorder, when the insomnia is interfering with normal daily life and other therapies (behavioural and pharmacologic) have failed. Treatment should be as an adjunct to behavioural therapy and sleep hygiene management. The use of Chloral Hydrate Oral Solution in children and adolescents is not generally recommended and if used should be under the supervision of a medical specialist.

4.2 Posology and method of administration

Conditions for Use:

The treatment should be as short as possible and should not exceed the maximum treatment period of 2 weeks.

Repeat courses of chloral hydrate are not recommended and can only be administered following medical specialist re-assessment, since the risk of abuse and dependence increases with the duration of treatment (see section 4.4).

Following prolonged treatment with chloral hydrate the dose should be slowly tapered before discontinuation.

The use of Chloral Hydrate Oral Solution in children and adolescents is not generally recommended and if used should be under the supervision of a medical specialist (see section 4.1).

Posology

Chloral Hydrate 500mg/5ml Oral Solution should be administered as a single daily dose, between 15 to 30 minutes before bedtime with water or milk.

Adults:

The usual dose is 430-860 mg (4.3-8.6 ml of the 500mg/5ml strength). Higher doses should not exceed a maximum of 2 g chloral hydrate (20 ml of the 500mg/5ml strength) per dose.

Elderly:

Dosage as for adults, except for the frail elderly or those with hepatic impairment where a reduction in dose may be appropriate (see section 4.4).

Paediatric population

Children 12 years and over

The usual dose is 430-860 mg (4.3-8.6 ml of the 500mg/5ml strength). Higher doses should not exceed a maximum of 2 g chloral hydrate (20 ml of the 500mg/5ml strength) per dose.

Children (between 2 and 11 years):

30-50 mg/kg (0.3-0.5 ml/kg of the 500mg/5ml strength) of bodyweight. The dose should not exceed 1 g chloral hydrate (10 ml of the 500mg/5ml strength) per dose.

Children under 2 years:

Chloral hydrate should not be used because the safety and efficacy of chloral hydrate in children aged under 2 years has not been established (see sections 4.4).

Hepatic impairment:

Chloral hydrate is contraindicated in patients with severe hepatic impairment (see section 4.3). Specific guidelines for dosage adjustments in mild and moderate hepatic impairment are not available; chloral hydrate is extensively metabolized by the liver and, therefore, dose adjustments may be warranted.

Renal impairment:

Chloral hydrate is contraindicated in patients with renal failure or severe renal impairment (see section 4.3). Specific guidelines for dosage adjustments in mild and moderate renal impairment are not available; dose adjustments may be warranted.

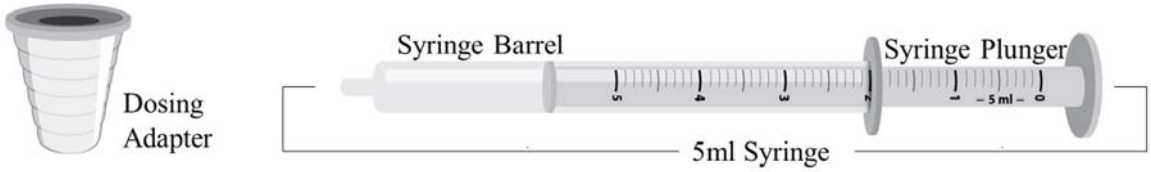
Method of administration

Oral.

Chloral Hydrate 500mg/5ml Oral Solution does not require dilution.

Directions for Chloral Hydrate 500mg/5ml Oral Solution

The box containing this medicine will contain a 5 ml dosing syringe and a dosing adapter.

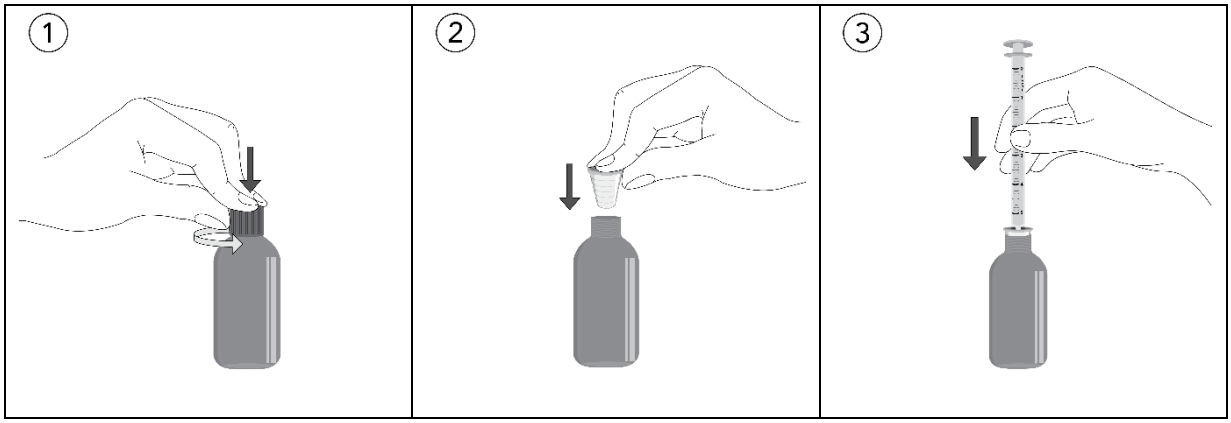


Instructions are provided below for using the dosing syringe.

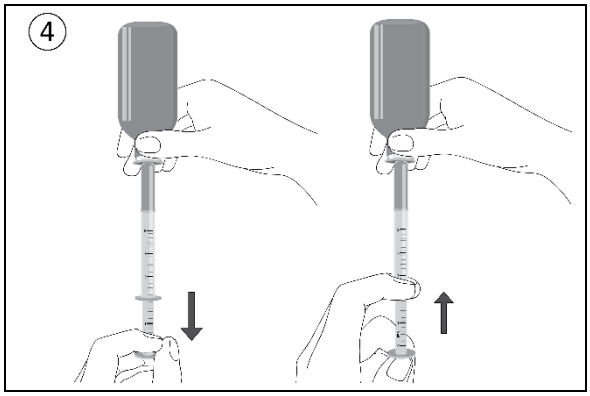
If you have any questions about how to use the syringe, you should ask your doctor, pharmacist, or nurse.

Instructions for use:

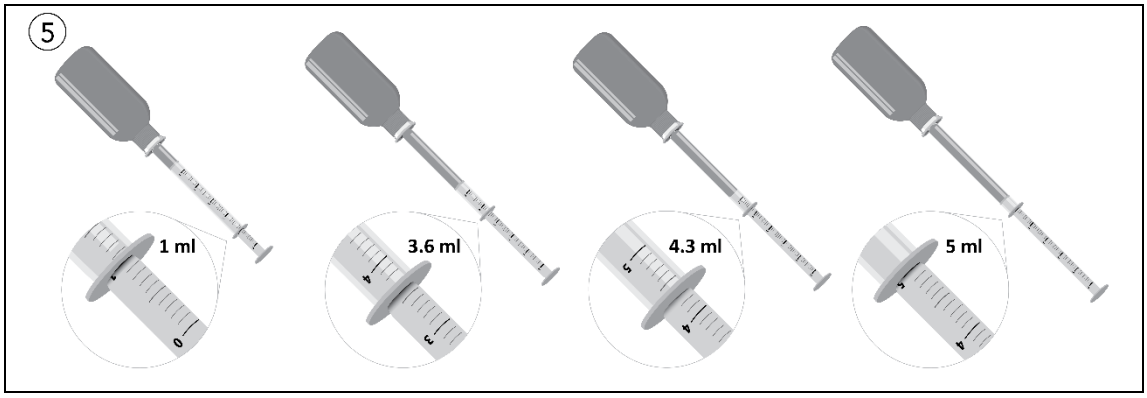
- Open the bottle: press the cap and turn it anticlockwise (see figure 1).
- Holding the bottle, take the plastic syringe adapter from the box and insert the adapter firmly into the bottle neck (see figure 2).
- Take the syringe and put it in the adapter opening (see figure 3).



- Turn the bottle upside down and fill the syringe with a small amount of solution by pulling the plunger down (see figure 4), then push the plunger upward in order to remove any possible bubbles.

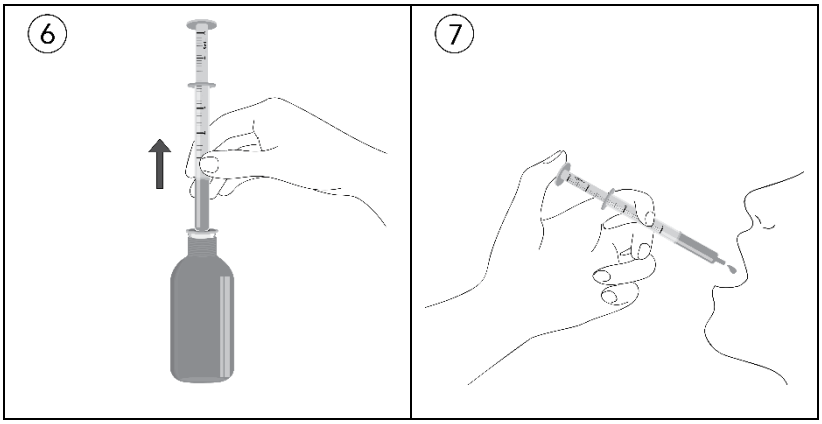


- Pull the plunger down to the graduation mark corresponding to the quantity in millilitres (ml) prescribed by your doctor (see figure 5 which represents examples of measuring dose of 1 ml, 3.6 ml, 4.3 ml and 5 ml).



- Turn the bottle the right way up. Remove the syringe from the adapter (see figure 6).

- Administer the contents of the syringe into the mouth by pushing the plunger to the bottom of the syringe (see figure 7), and ensure that the medicine is swallowed.



After use

Remove the adapter from the bottle and close the bottle with the plastic screw cap. Wash the adapter and syringe with warm water. Dry and replace them into the box with your medicine.

4.3 Contraindications

- Hypersensitivity to chloral hydrate or to any of the excipients listed in section 6.1.
- in patients with severe hepatic impairment,
- in patients with severe renal impairment,
- in patients with severe cardiac disease,
- in patients with active gastritis, oesophagitis, gastric or duodenal ulcers or perforation,
- in patients susceptible to acute attacks of porphyria.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2).

Tolerance, dependence, withdrawal, misuse

Tolerance, dependence and withdrawal symptoms have been reported with chloral hydrate. Abrupt discontinuation should not be undertaken in patients receiving prolonged treatment with chloral hydrate. Sudden withdrawal of the drug may cause delirium and hallucinations. Slowly withdraw chloral hydrate.

Individuals with a history of alcohol or drug abuse or dependence may be at greater risk for abuse and misuse of chloral hydrate. Prior to prescribing chloral hydrate, each patient's risk for abuse or misuse should be assessed and patients receiving chloral hydrate should be monitored for the development of behaviours or conditions of abuse or misuse while on therapy.

Gastrointestinal disorders

Chloral hydrate should be used with caution in patients with history of gastritis, oesophagitis, gastric or duodenal ulceration or perforation. Chloral hydrate is contraindicated in patients with active gastritis, oesophagitis, gastric or duodenal ulcers or perforation (see section 4.3).

Hepatic and renal impairment

Chloral hydrate should be used with caution in patients with mild to moderate hepatic and renal impairment and is contraindicated in patients with severe hepatic and renal impairment (see sections 4.2 and 4.3).

Elderly patients

Elderly patients are more likely to experience the undesirable effects of hypnotics such as ataxia and confusion which may lead to falls and injury. For use in the frail elderly, it is recommended that the lowest effective dose be administered (see section 4.2 and 4.5).

QT prolongation

Chloral hydrate should be used with caution and particular care in patients with low potassium levels, bradyarrhythmia, congenital long QT syndrome and other heart disorders (especially arrhythmia) (see sections 4.5 and 4.8).

Paediatric population

Due to immaturity of hepatic metabolism in neonates and children <2 years of age, there is a risk of extended half-life of chloral hydrate and increased risk of undesirable effects (see section 5.2).

Excipient warnings in the formulation

Liquid Glucose: Patients with rare glucose-galactose malabsorption should not take this medicine.

Sodium benzoate: This medicine contains 6.3 mg of sodium benzoate in each 5 ml, which is equivalent to 1.26 mg/ml. Sodium benzoate may increase bilirubinaemia in neonates, resulting in neonatal jaundice which may develop into kernicterus.

Propylene glycol: This medicine contains 18.39 mg propylene glycol in each 5 ml which is equivalent to 3.678 mg/ ml. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

Glycerol: May cause headache, stomach upset and diarrhoea.

This medicine contains less than 1 mmol sodium (23 mg) per 5 ml, which is to say it is essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No formal assessments of pharmacokinetic interactions between chloral hydrate and other therapeutic medicinal products have been conducted.

Concomitant use of alcohol and chloral hydrate may potentiate the sedative effect; concomitant use should be avoided.

In combination with CNS depressants an enhancement of the central depressive effect may occur. Concomitant use with antipsychotics, hypnotics, anxiolytics/sedatives, antidepressant agents, centrally acting muscle relaxants, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines should be avoided.

The concomitant use of drugs that also prolong the QT interval in ECG (for example, antiarrhythmics of Class IA or III, antibiotics, agents against malaria, H1 antihistamines, antipsychotics or medicinal products known to cause hypokalaemia or hypomagnesaemia) can lead to cardiac arrhythmias (see sections 4.4 and 4.8).

Chloral hydrate followed by intravenous furosemide may result in sweating, hot flushes and variable blood pressure including hypertension due to a hypermetabolic state caused by displacement of thyroid hormone from its bound state.

Delirium may occur, especially in the elderly, particularly when used in conjunction with psychotropics or anticholinergics.

In patients taking anticoagulants, when chloral hydrate is added to or withdrawn from the drug regimen, or its dosage changed, careful monitoring of the prothrombin time is required.

Chloral hydrate may interfere with laboratory tests of thyroid function.

4.6 Fertility, pregnancy and lactation

Chloral hydrate oral solution should not be used in pregnancy and lactation.

Pregnancy

Little information is available on the possible adverse effects of chloral hydrate on human pregnancy. Chloral hydrate is known to cross the human placenta at term, but its use during relatively few pregnancies did not cause a detectable increase in abnormal outcomes. Some data suggest that prolonged administration of sedative doses of chloral hydrate to neonates increases the likelihood of hyperbilirubinemia.

Breast Feeding

Low levels of chloral hydrate have been found in breast milk. Although breastfeeding infants may be sedated by chloral hydrate in breast milk, the highest concentration measured in the milk (about 15 µg/ml) was considerably lower than that which would be measured in blood at a clinically active dose (100 µg/ml).

Fertility

There is no information relating to the effects of Chloral Hydrate Oral Solution on fertility.

4.7 Effects on ability to drive and use machines

Patients receiving Chloral Hydrate Oral Solution should be warned that their ability to drive or use machinery may be impaired by drowsiness.

4.8 Undesirable effects

The following adverse reactions have been reported. The frequency grouping is defined using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Immune system disorders:	Not known: hypersensitivity, allergic skin reactions

Metabolism and nutrition disorders:	Not known: ketonuria
Psychiatric disorders:	Not known: anxiety, hyperactivity, confusion, tolerance, dependence, delirium, abuse, chronic intoxication, withdrawal symptoms
Nervous system disorders:	Not known: headache, ataxia
Respiratory, thoracic and mediastinal disorders:	Not known: dyspnoea, respiratory depression
Cardiac disorders:	Not known: QTc prolongation, arrhythmias (see sections 4.4 and 4.5)
Gastrointestinal disorders:	Not known: gastric irritation, abdominal distension, flatulence, gastric necrosis, gastric perforation, nausea, vomiting, gastritis
Renal and urinary disorders:	Not known: parenchymatous renal injury

Elderly patients

Ataxia, confusion, falls and injuries.

Paediatric population

In neonates and children <2 years of age, there is an increased risk of undesirable effects (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions *via* the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The signs and symptoms of overdose involve the cardiovascular, respiratory and central nervous system. These may include respiratory depression, arrhythmias, hypothermia, pin-point pupils, hypotension, or coma. Gastric irritation may result in vomiting and even gastric necrosis. If the patient survives, icterus due to hepatic damage and albuminuria from renal damage may appear. Serious problems have arisen with doses as little as 4 g and 10 g can be fatal. Overdosage should be treated with gastric lavage or inducing vomiting to empty the stomach. Supportive measures must be used. Haemodialysis, and in some cases haemoperfusion, have been reported to be effective in promoting the clearance of trichloroethanol.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and Sedatives, ATC code – N05CC01

Chloral hydrate is a derivative of chloral, which leads to a decrease in sleep latency and in the number of awakenings. A near natural sleep is induced and the REM/Non-REM ratio is not altered.

Mechanism of action

Chloral hydrate has been used for a great many years as a sedative/hypnotic drug in human and veterinary medicine. The metabolite (trichloroethanol) is responsible for the pharmacological effect. The proposed mechanisms for the depression of the central nervous system include potentiating the function of GABAA receptors, inhibition of excitatory amino acid-activated currents mediated by *N*-methyl-D-aspartate, and allosteric modulation of the 5- hydroxytryptamine 3 receptor-mediated depolarization of the vagus nerve.

5.2 Pharmacokinetic properties

Absorption:

Chloral hydrate is rapidly absorbed from the gastrointestinal tract and starts to act within 30 minutes of oral administration. The duration of action is for between 4 to 8 hours. Plasma concentrations of chloral hydrate (or the major metabolite trichloroethanol) required for sedative or hypnotic effects are unknown.

Distribution:

Chloral hydrate is widely distributed throughout the body, as is the active metabolite trichloroethanol. Both have been detected in the CSF, umbilical cord blood, foetal blood and amniotic fluid. The active metabolite is 70% to 80% protein bound. Following therapeutic doses of chloral hydrate, only small amounts of the clinically active metabolite is distributed into breast milk.

Metabolism:

Chloral hydrate is rapidly metabolised by the liver, erythrocytes, and other tissues to form trichloroethanol (an active metabolite). The reduction of chloral hydrate to trichloroethanol is catalysed by alcohol dehydrogenase and other enzymes. The plasma half-life of trichloroethanol is about 4 to 12 hours. This is increased to between 1 to 2 days in neonates. A small but variable amount of chloral hydrate and a larger portion of trichloroethanol are oxidised to trichloroacetic acid (an inactive metabolite) in the liver and kidneys. Trichloroethanol may also be conjugated to form trichloroethanol glucuronide, another inactive metabolite.

Other metabolites of chloral hydrate such as trichloroacetic acid and dichloroacetate are inactive metabolites, and produced in small quantities which are not anticipated to produce any safety concerns during short-term use.

Excretion:

The metabolites of chloral hydrate are slowly excreted in the urine. Some metabolites may also be excreted into the bile and faeces. Chloral hydrate is not excreted in the urine unchanged. The quantities of metabolites excreted in the urine may vary between individuals, as well as in the same individual on different days.

Paediatric population

Because of the immaturity of hepatic metabolism, particularly the glucuronidation pathway and decreased glomerular filtration in infants, the half-life of trichloroethanol is increased in neonates and children <2 years of age compared to older children and adults (see Sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

Chloral hydrate induces liver tumours in male mice, with no tumourigenic effects in rats. The mechanism of tumour induction is not known, but in the absence of clear evidence of mutagenic and clastogenic potential, it is unlikely to be relevant in man.

There are no controlled studies on toxicity to humans following extended exposure to chloral hydrate. Studies in laboratory animals demonstrate that liver is a target tissue and hepatocellular tumours have been observed in male mice and adenomas in the pituitary gland *pars distalis* in female mice after chronic, high-dose administration. No tumours occurred in rats after chronic high-dose administration. Slight effects are also observed in some studies in laboratory animals on sperm motility, developmental neurotoxicity (passive avoidance learning), and humoral immunity. All of the adverse effects noted in studies in laboratory animals occur at an exposure that is greater than the recommended clinical dose for sedation in humans.

Chloral hydrate did not cause meiotic delay in the oocytes of adult mice when administered at the time of resumption of maturation induced by hormones. It did cause adverse effects *in vitro* when a synchronized population of oocytes was exposed prior to resumption of maturation.

There was a slight depression in humoral and cell-mediated immunity in female CD1 mice exposed for 90 days to chloral hydrate in the drinking water. However, other data on haemagglutination titre and survival in chronic rodent bioassays indicate that immunosuppressive effects are unlikely.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E 422)

Liquid glucose

Citric acid (E 330)

Sodium citrate (E 331)

Sodium benzoate (E 211)

Saccharin sodium (E 954)

Essence of passion fruit [containing natural flavouring, artificial flavouring, propylene glycol (E1520)]

Purified water

6.2 Incompatibilities

None known.

6.3 Shelf life

Unopened: 12 months when stored below 25°C.

Once opened: 28 days.

6.4 Special precautions for storage

Store below 25° C. Keep the bottle upright in outer carton in order to protect from light.

6.5 Nature and contents of container

Amber glass bottle with screw cap (polypropylene/HDPE/LDPE), containing 150 ml of Chloral Hydrate Oral Solution, presented in a carton.

Each pack also contains a 5 ml oral syringe (polypropylene body, HDPE plunger) with intermediate graduations of 0.1 ml, and syringe adapter (LDPE).

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Marlborough Pharmaceuticals Ltd.,

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Miles Gray Road,

Basildon, Essex SS14 3FR,

United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 23138/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/06/2021

10 DATE OF REVISION OF THE TEXT

12/09/2022