Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Chloral Hydrate 500mg/5ml Oral Solution

(chloral hydrate)

PL 23138/0021

Marlborough Pharmaceuticals Ltd

LAY SUMMARY

Chloral Hydrate 500mg/5ml Oral Solution (chloral hydrate)

This is a summary of the Public Assessment Report (PAR) for Chloral Hydrate 500mg/5ml Oral Solution. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Chloral Hydrate Oral Solution in this lay summary for ease of reading.

For practical information about using Chloral Hydrate Oral Solution, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Chloral Hydrate Oral Solution and what is it used for?

This application is for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the UK for at least 10 years, with recognised efficacy and an acceptable level of safety.

Chloral Hydrate Oral Solution is used in:

Adults:
Chloral Hydrate Oral Solution is used for the short-term (maximum 2 weeks) treatment of severe sleeplessness (insomnia) which is interfering with normal daily life and where non-drug therapies (such as behavioural therapy and sleep hygiene) and other drugs have failed. Chloral Hydrate Oral Solution should be used in addition to non-drug therapies.

Children and adolescents aged 2 years and above:
Chloral Hydrate Oral Solution is used for the short-term (maximum 2 weeks) treatment of severe sleeplessness (insomnia) in children and adolescents with suspected or definite disorders that affect the development of the neurological system and brain (neurodevelopmental disorder). It is only used when the sleeplessness interferes with normal daily life and other therapies (non-drug therapies and other drugs) have failed. Chloral Hydrate Oral Solution should be used in addition 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.

How does Chloral Hydrate Oral Solution work?

Chloral Hydrate Oral Solution contains chloral hydrate which is one of a group of medicines called hypnotics (sleep inducing drugs).

How is Chloral Hydrate Oral Solution used?

The pharmaceutical form of this medicine is an oral solution and the route of administration is oral (via the mouth).

For Chloral Hydrate Oral Solution to work successfully, the patient's doctor will need to identify the most appropriate dose for treating their sleeplessness. Chloral Hydrate Oral Solution is available in two strengths (500mg/5ml and 143mg/5ml). The patient's doctor will help them to select the most appropriate strength and dose.

Chloral Hydrate Oral Solution should be taken as a single daily dose, 15-30 minutes before bedtime, with water or milk.

The usual recommended doses for Chloral Hydrate 500mg/5ml Oral Solution are:
Adults and Children aged 12 years and over and the Elderly:
The usual starting dose is 430 - 860 mg (4.3 - 8.6 ml of the 500mg/5ml strength).

In the frail elderly or patients with liver problems, a smaller dose may be required.

Not more than 20 ml of the 500mg/5ml strength Chloral Hydrate Oral Solution (equivalent to 2 g of chloral hydrate) should be taken in any one day.

Children 2 - 11 years:
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. The dose will be calculated by the patient's doctor or pharmacist based on the weight of the child. The patient's care giver should follow their doctor or pharmacist's instructions. **Not more than 10 ml of the 500mg/5ml strength Chloral Hydrate Oral Solution (equivalent to 1 g of chloral hydrate) should be taken in any one day.**

For further information on how Chloral Hydrate Oral Solution is used, including the method of administration, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Chloral Hydrate Oral Solution have been shown in studies?
Chloral Hydrate Oral Solution is a line extension of the existing product Welldorm Elixir / Chloral Hydrate 143mg / 5ml Elixir. The data submitted previously for Welldorm Elixir / Chloral Hydrate 143mg / 5ml Elixir and the new literature references to support this higher strength application for the active chloral hydrate (500 mg / 5 ml) are sufficient to demonstrate that Chloral Hydrate Oral Solution shows a benefit in the indications listed.

What are the possible side effects of Chloral Hydrate Oral Solution?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Chloral Hydrate Oral Solution is a line extension of the existing product Welldorm Elixir / Chloral Hydrate 143mg per 5ml Elixir, its benefits and possible side effects are taken as being the same as Welldorm Elixir / Chloral Hydrate 143mg per 5ml Elixir.

Why was Chloral Hydrate Oral Solution approved?
It was concluded that, as Chloral Hydrate Oral Solution is a line extension of Welldorm Elixir / Chloral Hydrate 143mg / 5ml Elixir, the indications and side effects observed with Welldorm Elixir / Chloral Hydrate 143mg / 5ml Elixir are applicable to Chloral Hydrate Oral Solution. Therefore, the MHRA decided that, as for Welldorm Elixir / Chloral Hydrate 143mg / 5ml Elixir, the benefits are greater than the risks and recommended that Chloral Hydrate Oral Solution can be approved for use.

What measures are being taken to ensure the safe and effective use of Chloral Hydrate Oral Solution?
A Risk Management Plan (RMP) has been developed to ensure that Chloral Hydrate Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Chloral Hydrate Oral Solution
A Marketing Authorisation for Chloral Hydrate Oral Solution was granted in the United Kingdom (UK) on 15 June 2021

The full PAR for Chloral Hydrate Oral Solution follows this summary.

This summary was last updated in September 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Chloral Hydrate 500mg/5ml Oral Solution (23138/0021) could be approved.

The product is approved for the following indications:
Adults:
Chloral Hydrate 500mg/5ml 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 500mg/5ml 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.

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.

This application was submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as a well-established use application. No new non-clinical or clinical studies were submitted, as the data submitted for this application is in the form of literature references. As this application is for a line extension of the existing product Welldorm Elixir / Chloral Hydrate 143mg / 5ml Elixir, the non-clinical and clinical data are identical to those submitted previously. The Applicant also submitted bibliographic data to support the pharmacokinetics, efficacy and safety of the proposed adult /children of 12 years and over dose range of 500 - 1000 mg for this higher strength line extension application. The Applicant has also provided suitable justification to bridge the data from the bibliography to the current formulation proposed.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 11 - 12 May 2017 and as a result of its consideration was of the opinion that on the grounds relating to quality, safety and efficacy it may be unable to advise the licensing authority to grant the authorisation. In response, the Applicant submitted further quality, safety and efficacy data for the medicinal product as a written representation addressing these concerns for which

advice was sought by the CHM on 06 – 07 May 2021. The submitted data were deemed acceptable and a national marketing authorisation was granted in the United Kingdom (UK)on 15 June 2021.

II QUALITY ASPECTS

II.1 Introduction

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

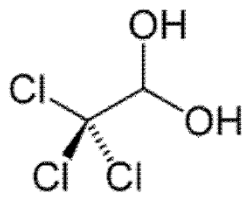
In addition to chloral hydrate, this product also contain the excipients glycerol (E422), liquid glucose, citric acid (E330), sodium citrate (E331), sodium benzoate (E211), saccharin sodium (E954), essence of passion fruit [containing natural flavouring, artificial flavouring, propylene glycol (E1520)] and purified water.

The finished product is packaged in amber glass bottles with a screw cap (polypropylene/HDPE/LDPE), containing 150 ml of Chloral Hydrate 500mg/5ml 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).

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 Chloral hydrate

rINN: Chloral hydrate
Chemical Name: 2,2,2-Trichloroethane-1,1-diol
Molecular Formula: $C_2H_3Cl_3O_2$
Chemical Structure: >



Molecular Weight: 165.4
Appearance: Colourless, transparent crystals
Solubility: Very soluble in water, freely soluble in ethanol (96 percent).

Chloral hydrate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 6 months with the storage conditions ‘Store below 25° C. Keep the bottle upright in outer carton in order to protect from light’ for the unopened bottle, is acceptable. The in-use shelf life is 28 days once the bottle is opened.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

This application was submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended, as a well-established use application. No new non-clinical studies were submitted, as the data submitted for this application is in the form of literature references. As this application is for a line extension of the existing product Welldorm Elixir / Chloral Hydrate 143mg / 5ml Elixir, the non-clinical data are identical to those submitted previously. The Applicant has also provided data to support the effects relating to non-clinical pharmacology, pharmacokinetics and toxicology of chloral hydrate for the new strength and treatment regime in the proposed patient population.

III.2 Pharmacology

With the exception of literature submitted to support the new strength and treatment regime in the proposed patient population in this line extension application, no new pharmacology data were submitted, and none were required for this application.

III.3 Pharmacokinetics

With the exception of literature submitted to support the new strength and treatment regime in the proposed patient population in this line extension application, no new pharmacokinetics data were submitted, and none were required for this application.

III.4 Toxicology

The Applicant cited the relevant data from the literature to support the toxicological effects of chloral hydrate, summarised as follows in the approved SmPC:

"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."

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a product containing an active substance of well-established use that will be used in place of existing products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

As this application is for a line extension of the existing product Welldorm Elixir / Chloral Hydrate 143mg / 5ml Elixir, the clinical data are identical to those submitted previously. Thus, with the exception of the bibliographic data submitted to support the pharmacokinetics of the proposed higher strength product and the suitable justification to bridge the data from the bibliography to the current formulation proposed, no new clinical data were submitted and none were required.

The palatability of the final higher strength formulation was also investigated. The taste remained acceptable.

IV. 2 Pharmacokinetics

The Applicant cited the relevant data from the literature to support the pharmacokinetic effects of chloral hydrate, summarised as follows in the approved SmPC:

"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)."

IV.3 Pharmacodynamics

The Applicant cited the relevant data from the literature to support the pharmacodynamic effects of chloral hydrate, summarised as follows in the approved SmPC:

"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."

IV.4 Clinical efficacy

With the exception of literature submitted to support the new strength and treatment regime in the proposed patient population in this line extension application, no new efficacy data were submitted, and none were required for this application.

IV.5 Clinical safety

With the exception of literature submitted to support the new strength and treatment regime in the proposed patient population, no new safety data were submitted with this application and none were required. The safety profile for this product is considered to be the same as Welldorm Elixir / Chloral Hydrate 143mg / 5ml Elixir.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted a RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the

guideline on the readability of the label and package leaflet of medicinal products for human use.

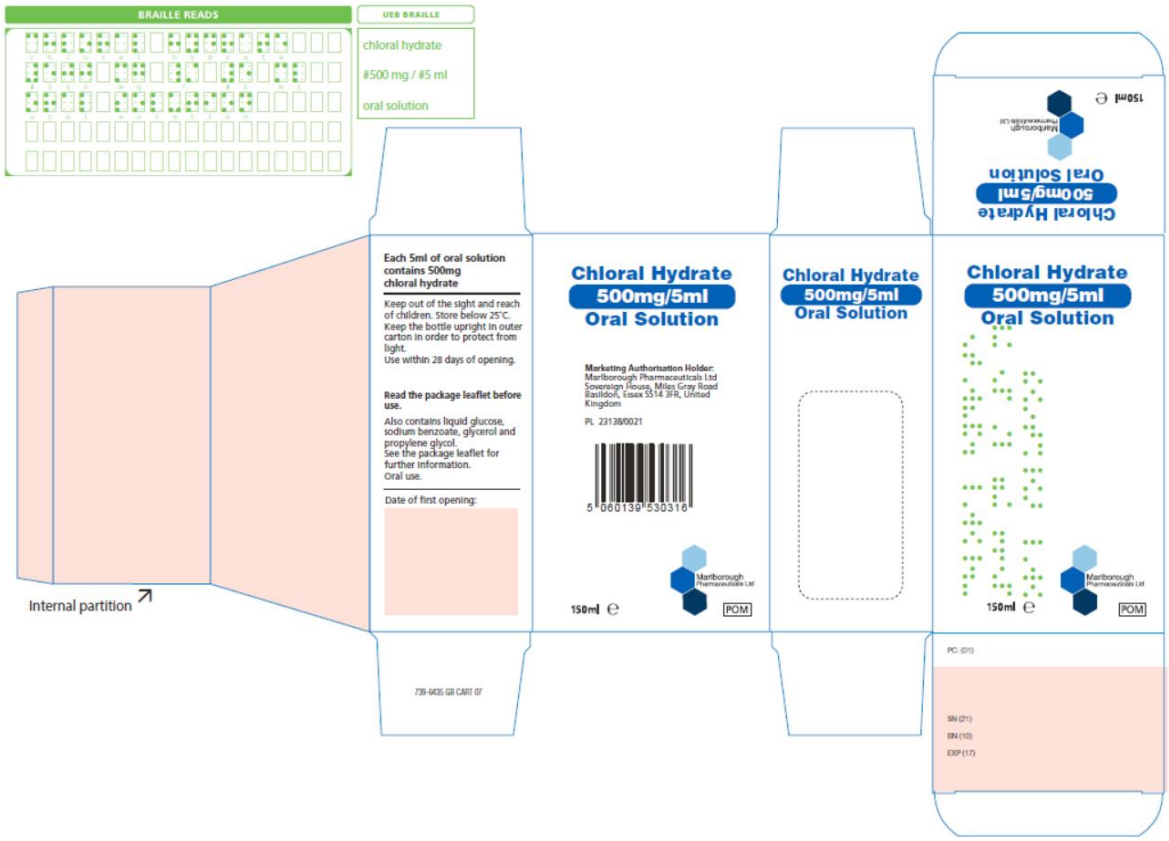
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

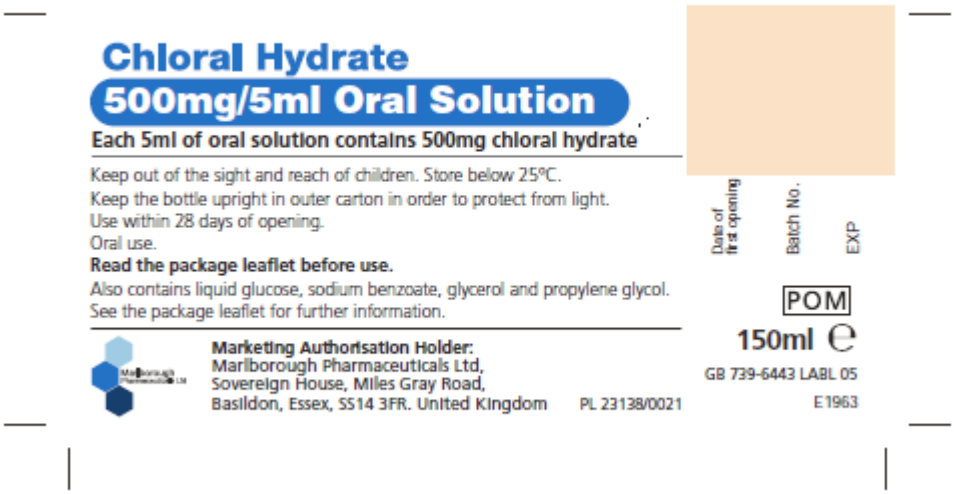
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with chloral hydrate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the current approved labels are provided below.




Chloral Hydrate
500mg/5ml Oral Solution
Each 5ml of oral solution contains 500mg chloral hydrate
Keep out of the sight and reach of children. Store below 25ºC.
Keep the bottle upright in outer carton in order to protect from light.
Use within 28 days of opening.
Oral use.
Read the package leaflet before use.
Also contains liquid glucose, sodium benzoate, glycerol and propylene glycol.
See the package leaflet for further information.
Marketing Authorisation Holder:
Marlborough Pharmaceuticals Ltd,
Sovereign House, Miles Gray Road,
Basildon, Essex, SS14 3FR. United Kingdom
PL 23138/0021
Date of first opening
Batch No.
EXP
POM
150ml
GB 739-6443 LABL 05
E1963

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**