UKPAR  Chloral Hydrate 143.3mg in 5ml Oral Solution
PL 21600/0001

UKPAR

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LAY SUMMARY

The MHRA granted Huntley Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Chloral Hydrate 143.3 mg in 5 ml Oral Solution (PL 21600/0001) on 20th March 2007. This prescription-only medicine (POM) is used in the short-term treatment of insomnia.

The active ingredient, chloral hydrate is one of a group of medicines called hypnotics that induces sleep and act on the central nervous system.

This application is identical to a previously granted application for Welldorm Elixir (PL 13374/0005, granted to Smith & Nephew Pharmaceutical Limited on 30th December 1993.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Chloral Hydrate 143.3 mg in 5 ml Oral Solution outweigh the risks; hence a Marketing Authorisation has been granted.

The licence for this product was cancelled on 15th September 2007.
CHLORAL HYDRATE 143.3 MG IN 5ML ORAL SOLUTION  
PL 21600/0001

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Chloral Hydrate 143.3 mg in 5 ml Oral Solution (PL 21600/0001) to Huntley Pharmaceuticals Limited on 20th March 2007. The product is a prescription-only medicine.

The application was submitted as a simple abridged application according to Article 10c of Directive 2001/83/EC, cross-referring to Welldorm Elixir (PL 13374/0005) currently authorised to Smith & Nephew Pharmaceuticals Limited, UK following a change of ownership. The reference product has been authorised in the UK since December 1993 and so the 10-year period of data exclusivity has expired.

No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) has been generated for it.

The product contains the active ingredient choral hydrate which is a hypnotic drug which acts on the central nervous system and used in the short-term treatment of insomnia.

The licence for this product was cancelled on 15th September 2007.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 21600/0001
PROPRIETARY NAME: Chloral Hydrate 143.3 mg in 5 ml Oral Solution
ACTIVE(S): Chloral hydrate
COMPANY NAME: Huntley Pharmaceuticals Limited
LEGAL STATUS: POM

1. INTRODUCTION
This is a simple, informed consent application for Chloral Hydrate 143.3 mg in 5 ml Oral Solution submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Huntley Pharmaceutical Limited, 35A High Street, Marlborough, Wiltshire, SN8 1LW, UK.

The application cross-referes to Welldorm Elixir, approved on 30th December 1993 to the marketing authorisation holder Smith & Nephew Pharmaceuticals Limited. The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)
The proposed name of the product is Chloral Hydrate 143.3 mg in 5 ml Oral Solution. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The product contains chloral hydrate, equivalent to 143.3 mg per 5 ml of solution. It is to be stored in amber glass bottles with child proof plastic screw caps. The proposed shelf-life (30 months) and storage conditions (“Do not store above 25°C. Store in the original package” and “Keep the bottle in the outer carton”) are consistent with the details registered for the cross-reference product.

2.3 Legal status
On approval, the product will be available as prescription-only medicine (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
Huntley Pharmaceutical Limited, 35A High Street, Marlborough, Wiltshire, SN8 1LW, UK.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.
2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

2.10 TSE Compliance
No materials of animal and/or human origin are contained or used in the manufacturing process for the medicinal product. This is consistent with the cross-reference product.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summary is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON
   PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.
The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

   Carton
The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the application are acceptable. A Marketing Authorisation should be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
Chloral hydrate is a well known drug and has been used as a hypnotic drug for many years. This application is identical to previously granted application for Welldorm Elixir (PL 13374/0005) granted to Smith & Nephew Pharmaceuticals Limited. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product which, in turn, has been shown to be interchangeable with the innovator product. Extensive clinical experience with chloral hydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.
CHLORAL HYDRATE 143.3 MG IN 5 ML ORAL SOLUTION
PL 21600/0001

STEPS TAKEN FOR ASSESMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 29\textsuperscript{th} July 2004.</td>
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<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 30\textsuperscript{th} November 2005.</td>
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<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 12\textsuperscript{th} October 2006.</td>
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<td>The applicant responded to the MHRA’s requests, providing further information on 13\textsuperscript{th} March 2007.</td>
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<td>The application was determined on 20\textsuperscript{th} March 2007.</td>
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CHLORAL HYDRATE 143.3 MG IN 5ML ORAL SOLUTION
PL 21600/0001

STEPS TAKEN AFTER ASSESSMENT

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CHLORAL HYDRATE 143.3 MG IN 5ML ORAL SOLUTION
PL 21600/0001

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Chloral Hydrate 143.3 mg in 5 ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5ml of Chloral Hydrate Oral Solution contains 143.3 mg of Chloral Hydrate.

For excipients see 6.1

3. PHARMACEUTICAL FORM
Oral Solution

Clear red oral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Chloral Hydrate 143.3 mg in 5 ml Oral Solution is used for the short-term treatment of insomnia.

4.2 Posology and Method of administration

Adults: 15-45 ml taken 15-30 minutes before bedtime with water or milk. Dose should not exceed 2g chloralhydrate per day.

Elderly: Dosage as for adults except for the frail elderly or those with hepatic impairment, where a reduction in dose may be appropriate.

Children: 30-50mg/kg of bodyweight. Dose should not exceed 1g chloral hydrate per day.

4.3 Contra-Indications
Hypersensitivity to the active substance or to any of the excipients (see 6.1).

Chloral Hydrate 143.3 mg in 5 ml Oral Solution should not be used in patients with marked hepatic or renal impairment, or in patients with severe cardiac disease, or in patients susceptible to acute attacks of porphyria.

4.4 Special Warnings And Special Precautions For Use
Best avoided in the presence of gastritis and in patients who have previously exhibited an idiosyncrasy or hypersensitivity to chloral hydrate.

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

4.5 Interactions with other Medicinal Products and other Forms of Interaction
Alcohol potentiates the sedative effect. 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. Delerium 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.

4.6 Pregnancy and Lactation
Chloral Hydrate 143.3 mg in 5 ml Oral Solution should not be used in pregnancy and lactation.

4.7 Effects on Ability to Drive and Use Machines
Patients receiving Chloral Hydrate 143.3 mg in 5 ml Oral Solution should be warned that their ability to drive or use machinery may be impaired by drowsiness.
4.8 Undesirable Effects
Gastric irritation, abdominal distension and flatulence may occur. Excitement, tolerance, allergic skin reactions, headache and ketonuria have occasionally been reported. There is a danger of abuse or chronic intoxication and the possibility that habituation may develop. In such patients gastritis and parenchymatous renal injury may develop. After long term use sudden withdrawal may result in delirium.

4.9 Overdose
The signs and symptoms of overdose involve the cardiovascular, respiratory and central nervous systems. 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 4g and 10g 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
Chloral Hydrate 143.3 mg in 5 ml Oral Solution is a chloral hydrate derivative, 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.

5.2 Pharmacokinetic Properties
Chloral hydrate and its metabolite trichloroethanol act as central nervous system depressants. Chloral hydrate is rapidly absorbed from the stomach, and starts to act within 30 minutes. It is widely distributed throughout the body, and is metabolised to trichloroethanol, also an active hypnotic, and trichloroacetic acid in the erythrocytes, liver and other tissues. It is excreted partly in the urine as trichloroethanol and its glucuronide, urochloralic acid, and as trichloroacetic acid. Significant amounts are also excreted in bile. Trichloroethanol has a plasma half life of the order of 8 hours. Trichloroacetic acid has a half-life of several days. In infants the half lives are longer. The value for trichloroethanol is 35 hours whilst for trichloroacetic acid the half life exceeds 6 days, with significant plasma concentrations present at 14 days.

5.3 Pre-clinical 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.

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
Glycerol
Liquid glucose
Sodium benzoate
Saccharin sodium
Sunset yellow FCF (E110)
Ponceau 4R (E124)
Essence of passion fruit containing natural and artificial flavouring, and propylene glycol (E1520)
Purified water

6.2 Incompatibilities
None known

6.3 Shelf-Life
30 months

6.4 Special Precautions for Storage
Store below 25°C. Store in the original packaging. Keep the bottle in the outer carton.
6.5 **Nature and Contents of Container**
Amber glass bottle with child-proof plastic screw cap, containing 150ml of Chloral Hydrate 143.3 mg in 5 ml Oral Solution, presented in a carton.

6.6 **Instructions for Use, Handling and Disposal**
Syrup BP should be used as a diluent.

7. **MARKETING AUTHORISATION HOLDER**
Huntley Pharmaceuticals Ltd
35A High Street
Marlborough
Wiltshire
SN8 1LW

8. **MARKETING AUTHORISATION NUMBER(S)**
PL 21600/0001

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
20/03/2007

10. **DATE OF REVISION OF THE TEXT**
20/03/2007
CHLORAL HYDRATE 143.3 MG IN 5ML ORAL SOLUTION
PL 21600/0001

PATIENT INFORMATION LEAFLET

What you should know about Chloral Hydrate 143.3mg in 5ml Oral Solution

Before using your medicine

Chloral Hydrate 143.3mg in 5ml Oral Solution contains Sunset Yellow FCF (E110) and Parabens (E211-213) which may cause allergic reactions.

If you have been told by your doctor that you have an allergy to any of these ingredients, please talk to your doctor about the risks involved in taking this medicine.

How to take your medicine

Chloral Hydrate 143.3mg in 5ml Oral Solution may cause drowsiness. Therefore, do not drive or operate machinery until you know how it affects you.

It is best if your medicine is taken with food or milk, but you can also take it with water if you find this easier.

You should use the before-use information provided on the packaging.

If you take too much of your medicine, contact your local hospital casualty department or your doctor immediately.

If you have any unexplained problems, contact your nearest hospital casualty department or your doctor immediately.

If you need to stop taking your medicine, contact your nearest hospital casualty department or your doctor immediately.

This medicine can cause side effects in some people. Some of these effects may be serious, and you should seek medical assistance if you experience any of them. For example:

Side effects that usually occur include:

- Drowsiness
- Nausea
- Vomiting
- Constipation
- Headache
- Dizziness

Side effects that may rarely occur include:

- A rash or skin condition
- A severe allergic reaction (anaphylaxis)
- A worsening of your illness

If you experience any of these side effects, contact your doctor or pharmacist immediately.

After taking your medicine

The manufacturer of this medicine cannot accept any liability for any loss or damage caused by its use. However, if you have any comments or suggestions about the use of this medicine, you may contact the manufacturer at the address provided.

Please note that this leaflet contains important information about the use of this medicine. Before starting this medicine, read the leaflet carefully and follow the instructions given by your doctor or pharmacist.

Date of preparation: 01/06/2005
CHLORAL HYDRATE 143.3 MG IN 5ML ORAL SOLUTION
PL 21600/0001

LABELLING

CARTON

Huntley Pharmaceuticals Ltd,
150 ml
Each bottle of Oral Solution contains 143.3mg Chlortal Hydrate
Store out of the sight and reach of children, Deep yellow C5
Steady state will be achieved after 3 days. Keep the bottle in the outer carton,
Not suitable for use in the elderly, or patients with liver damage.

Huntley Pharmaceuticals Ltd, 26A High Street, Marlborough, SN8 1LY
PL 21600/0001
Chlortal Hydrate 143.3mg in 5ml Oral Solution
CHLORAL HYDRATE