SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Heminevrin 31.5 mg/ml Syrup.

Clomethiazole 31.5 mg/ml Syrup.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clomethiazole edisilate 50 mg/ml (equivalent to 31.5 mg/ml of clomethiazole).

Excipients with known effect

Clomethiazole syrup contains 0.13 vol % of ethanol and less than 1 mmol sodium (23 mg) per dose. 1 ml of syrup contains 350 mg Sorbitol (E420).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Syrup.

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clomethiazole is a short acting hypnotic and sedative with anticonvulsant effect. It is used for the: management of restlessness and agitation in the elderly, short term treatment of severe insomnia in the elderly and treatment of alcohol withdrawal symptoms where close hospital supervision is also provided.

4.2 Posology and method of administration

Posology

Management of restlessness and agitation in the elderly: 5 ml of syrup three times daily.

Severe insomnia in the elderly: 5 - 10 ml of the syrup before going to bed. The lower dose should be tried first. As with all psychotropic drugs, treatment should be kept to a minimum, reviewed regularly and discontinued as soon as possible.

Alcohol withdrawal states: Clomethiazole is not a specific 'cure' for alcoholism. Alcohol withdrawal should be treated in hospital or, in exceptional circumstances, on an outpatient basis by specialist units when the daily dosage of Clomethiazole must be monitored closely by community health staff. The dosage should be adjusted to patient response. The patient should be sedated but rousable. A suggested regimen is:

Initial dose:	10 to 20 ml, if necessary repeated after some hours.
Day 1, first 24 hours:	45 - 60 ml, divided into 3 or 4 doses.
Day 2:	30 - 40 ml, divided into 3 or 4 doses.
Day 3:	20 - 30 ml, divided into 3or 4 doses.
Days 4 to 6:	A gradual reduction in dosage until the final dose.

Administration for more than nine (9) days is not recommended.

Paediatric population

The safety and efficacy of clomethiazole in children and adolescents under 18 years of age has not been established.

Method of administration

For oral use.

The syrup should be diluted with water or juice before use, then taken immediately. It must not be kept for later administration.

Clomethiazole edisilate is known for sorption to various plastic materials. Care should be taken during dilution and administration of clomethiazole syrup to avoid contact with plastic materials, or keep contact time to a minimum.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Acute pulmonary insufficiency.

4.4 Special warnings and precautions for use

Clomethiazole should be used cautiously in patients with sleep apnoea syndrome and chronic pulmonary insufficiency.

Clomethiazole may potentiate or be potentiated by centrally acting depressant drugs including alcohol and benzodiazepines. Fatal cardiorespiratory collapse has been reported when clomethiazole was combined with other CNS depressant drugs. When used concomitantly dosage should be appropriately reduced.

Hypoxia, resulting from, for example, cardiac and/or respiratory insufficiency, can manifest itself as an acute confusional state. Recognition and specific treatment of the cause is essential in such patients and in such cases sedatives/hypnotics should be avoided.

Moderate liver disorders associated with alcoholism do not preclude the use of clomethiazole, though an associated increase in systemic availability of oral doses and delayed elimination of the drug may require reduced dosage. Great caution should be observed in patients with gross liver damage and decreased liver function, particularly as sedation can mask the onset of liver coma.

Caution should be observed in patients with chronic renal disease.

Caution must be exercised in prescribing for individuals known to be addiction prone or for those whose histories suggest they may increase the dose on their own initiative since clomethiazole is not free from the risk of producing psychological and/or physical dependence. After prolonged administration of high doses, physical dependence has been reported with withdrawal symptoms such as convulsions, tremors, and organic psychosis. These reports have mainly been associated with indiscriminate prescribing to outpatient alcoholics and Clomethiazole should not be prescribed to patients who continue to drink or abuse alcohol.

Alcoholism: Alcohol combined with clomethiazole particularly in alcoholics with cirrhosis can lead to fatal respiratory depression even with short term use. It should not therefore be prescribed for alcoholics who continue to drink alcoholic beverages.

Elderly: Caution is advised as there may be increased bioavailability and delayed elimination of clomethiazole.

Clomethiazole syrup contains small amounts of ethanol (0.13 vol %). Each ml contains up to 1.04 mg of ethanol.One ml of Clomethiazole syrup contains 350 mg of sorbitol. When taken according to the dosage recommendations each dose supplies up to 7 g of sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine. May cause gastrointestinal discomfort and have a mild laxative effect.

4.5 Interaction with other medicinal products and other forms of interaction

Clomethiazole is an inhibitor of CYP2A6 and CYP2E1. The plasma clearance of CYP2E1 substrates may be decreased by clomethiazole. For CYP2El substrate chlorzoxazone, a threefold decrease of plasma clearance in patients has been shown in clinical studies. An influence on the metabolism is also possible for more clinically relevant CYP2El substrates including sedatives, anaesthetics, analgesics, antidepressants, antiepileptics and antibacterials. Co-administration of clomethiazole with CYP2E1 substrates may influence the pharmacokinetics of such drugs resulting in altered metabolism and therapeutic plasma levels. Therefore, a continuous and close monitoring of drug plasma levels is strongly recommended and potential dose adjustments of CYP2El-metabolized drugs may be required when used concomitantly with clomethiazole.

A combination of clomethiazole and diazoxide should be avoided as an adverse neonatal reaction suspected to be due to the maternal administration of this combination has been reported.

The combination of propranolol and clomethiazole has produced profound bradycardia in one patient possibly due to increased bioavailability of propranolol.

There is evidence to indicate that the metabolism of clomethiazole is inhibited by cimetidine, thus the co-administration of these drugs may lead to increased blood/plasma levels of clomethiazole.

When clomethiazole was administered by intravenous infusion in combination with carbamazepine, the clearance of clomethiazole increased by 30%, resulting in decreased plasma concentrations to the same extent. This interaction has not been studied after oral administration of clomethiazole. However, co-administration of carbamazepine and oral clomethiazole could result in both decreased bioavailability and increased clearance. Higher doses of clomethiazole could therefore be needed to obtain an effect when co-administered with carbamazepine or another potent inducer of the CYP3A4 enzyme.

4.6 Fertility, pregnancy and lactation

Pregnancy

Do not use in pregnancy especially during the first and last trimesters, unless there are compelling reasons. There is no evidence of safety in human pregnancy, nor is there evidence from animal studies that it is entirely free from hazard.

Breast-feeding

Clomethiazole is excreted into the breast milk. The effect of even small quantities of sedative/hypnotic and anticonvulsant drugs on the infant brain is not established.

Clomethiazole should only be used in nursing mothers where the physician considers that the benefit outweighs the possible hazard to the infant.

Fertility

There are no data on the effect of clomethiazole on fertility in humans.

4.7 Effects on ability to drive and use machines

Clomethiazole has major influence on the ability to drive and use machines.

As with all centrally acting depressant drugs, the driving of vehicles and the operating of machinery are to be avoided when under treatment.

4.8 Undesirable effects

The most common side-effect is nasal congestion and irritation, which may occur 15 to 20 minutes after drug ingestion. Conjunctival irritation has also been noted in some cases. Occasionally, these symptoms may be severe and may be associated with severe headache. This is commonest with the initial dose following which it decreases in severity with subsequent doses.

Immune system disorders

In rare cases anaphylactic reactions have occurred.

Psychiatric disorders

When clomethiazole has been given at higher than recommended doses for other than recommended indications over prolonged periods of time, physical dependence, tolerance and withdrawal reactions have been reported. Great caution is required in prescribing clomethiazole for patients with a history of chronic alcoholism, drug abuse or marked personality disorder.

Paradoxical excitement or confusion may occur rarely.

Nervous system disorders

Headache

Excessive sedation may occur, especially with higher doses or when given to the elderly for daytime sedation.

Eye disorders

Conjunctival irritation

Respiratory, thoracic and mediastinal disorders

Nasal congestion and irritation, increased nasopharyngeal/bronchial secretions can occur.

Gastrointestinal disorders

Gastrointestinal disturbances have been reported.

Hepatobiliary disorders

Reversible increases of transaminases or bilirubin have been reported.

Skin and subcutaneous tissue disorders

Rash and urticaria have been reported. In rare cases, bullous skin eruptions have been reported.

General disorders and administration site conditions

When used as a night-time hypnotic, hangover effects in the elderly may occur but are uncommon due to the short half-life.

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 main effects to be expected with overdose of clomethiazole are: coma, respiratory depression, hypotension and hypothermia.

Hypothermia is thought to be due to a direct central effect as well as a result of lying unconscious for several hours. In addition, patients have increased secretion in the upper airways, which in one series was associated with a high incidence of pneumonia. The effects of overdosage are not usually severe in patients with no evidence of alcoholic liver disease, but they may be exacerbated when clomethiazole is taken in combination with alcohol and/or CNS depressant drugs, particularly those that are metabolised by the liver. There is no specific antidote to clomethiazole. Treatment of overdosage should therefore be carried out on a symptomatic basis, applying similar principles to those used in the treatment of barbiturate overdosage.

Charcoal column haemoperfusion is not and cannot be expected to be effective in treating clomethiazole poisoning.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sedative/hypnotic and anticonvulsant, ATC code N05CM02

Clomethiazole is pharmacologically distinct from both the benzodiazepines and the barbiturates.

Clomethiazole has sedative, muscle relaxant and anticonvulsant properties. It is used for hypnosis in elderly and institutionalised patients, for preanaesthetic sedation and especially in the management of withdrawal from ethanol. Given alone its effects on respiration are slight and the therapeutic index high.

5.2 Pharmacokinetic properties

Clomethiazole has a short half-life, low oral bioavailability, high plasma clearance and shows no evidence of accumulation or altered pharmacokinetics after repeated dosage. It is excreted in urine after extensive metabolism in the liver. The rate of elimination is decreased by about 30% in liver cirrhosis.

5.3 Preclinical safety data

Extensive clinical use and experience with Clomethiazole has provided a well established safety profile for this drug.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid sorbitol (non-crystallising) (E420)

Cineole

Levomenthol

Ethanol

Sodium hydroxide

Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

After first opening the container: 120 days.

6.4 Special precautions for storage

Store in a refrigerator (2° to 8°C). Do not freeze.

Store in the original container. Do not transfer the syrup to another container since it may not be compatible with the container material (see section 4.2).

6.5 Nature and contents of container

300 ml amber glass type III bottle with a white polypropylene cap.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 45043/0034

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