SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Heminevrin 192 mg Capsules
Clomethiazole 192 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Clomethiazole 192 mg (base) per capsule.
10 mg Sorbitol (E420) per capsule.
For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Soft Capsules
Greyish-brown, soft gelatin capsules

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
For oral use.
The capsules should be swallowed whole.
Management of restlessness and agitation in the elderly: one capsule three times daily.
Severe insomnia in the elderly: 1 - 2 capsules 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: 2 to 4 capsules, if necessary repeated after some hours.
Day 1, first 24 hours: 9 to 12 capsules, divided into 3 or 4 doses.
Day 2: 6 to 8 capsules, divided into 3 or 4 doses.
Day 3: 4 to 6 capsules, divided into 3 or 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.

4.3 Contraindications
Known sensitivity to clomethiazole. 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.

Children: Oral clomethiazole is not recommended for use in children.
One capsule contains 10mg of sorbitol. When taken according to the dosage recommendations each dose supplies up to 40mg of sorbitol. Unsuitable in hereditary fructose intolerance.

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 CYP2E1 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 CYP2E1 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 CYP2E1-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
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.

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.
4.7 Effects on 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. Increased nasopharyngeal/bronchial secretions can occur.

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

Gastrointestinal disturbances have been reported.

Reversible increases of transaminases or bilirubin have been reported.

In rare cases anaphylactic reactions have occurred.

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.

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

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

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.

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
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 pre-anaesthetic 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
Medium-chain triglycerides, Gelatin, Glycerol (85%), Sorbitol (E420), Mannitol, Oligosaccharides, Titanium Dioxide (E171), Brown Iron Oxide (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Amber glass bottles: 24 months
Aluminium foil blister packs: 24 months

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original container.

6.5 Nature and contents of container
Amber glass bottle with white polyethylene child resistant clic-loc closure containing 60 or 100 capsules.
Transparent plastic bag in a cardboard outer for bulk packaging of 20,000 capsules.
Aluminium foil blister packs each containing 10 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
The capsules should remain in the container in which they are supplied.
The capsules should be swallowed whole.

7 MARKETING AUTHORISATION HOLDER
CHEPLAPHARM Arzneimittel GmbH
Bahnhofstr. 1a
17498 Mesekenhagen
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 27041/0001

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27/04/2017