Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Heminevrin 0.8% Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

8 mg/ml Clomethiazole edisilate.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Heminevrin is a short acting hypnotic and sedative with anticonvulsant effect used for the treatment of: pre-eclamptic toxaemia, eclampsia, acute withdrawal symptoms in alcoholics and drug addiction in hospital where oral administration is not practicable.

4.2 Posology and method of administration

For intravenous use.
When Heminevrin is given by i.v. infusion, the dosage should always be controlled by the desired effect and the patient's response. Exact recommendations on dosage cannot be given because of individual patient variation and the presence or absence of other CNS depressant drugs such as diazepam, paraldehyde or alcohol. The doses given below therefore are guides only and due account must be taken of the patient's age (i.e. children and the very elderly), the general condition and any previous medication.
In general, the infusion should be given as a loading dose to produce the required effect, followed by a maintenance dose. As is the case with intravenous anaesthetics, Heminevrin's brief action is due to redistribution of the drug and not to rapid elimination. Thus stopping the drug, will allow rapid reversal of its sedative effect initially but after large and prolonged dosage, recovery may be considerably delayed. The patient should be closely and constantly observed.

<u>Pre-eclamptic toxaemia</u>
Heminevrin is used to sedate the patient and raise the threshold for eclamptic convulsions.
It is indicated in moderate or severe pre-eclamptic toxaemia under the following circumstances: rapid progression of the disease, symptoms and signs associated with impending eclampsia, when labour is to be induced, during labour and post-partum (a) for up to 12 hours in patients with adequate urine output or (b) until recovery diuresis in patients with poor urinary output.
During labour most patients will require an average of 0.5 to 0.75ml/min of Heminevrin 0.8%. As the majority of patients are delivered within 24 hours, prolonged infusion is not necessary. Heminevrin has no analgesic properties and pain relief must be given as necessary. After delivery the intravenous infusion is maintained at 0.5ml/min for 12 hours. Thereafter oral therapy is continued.
When transferring to oral therapy, reference should be made to the Summary of Product Characteristics for Heminevrin capsules, in order to establish a suitable dose regular for each patient.

<u>Eclampsia</u>
Heminevrin is used to control eclamptic fits or to prevent their recurrence. It is used in conjunction with

antihypertensive drugs. If seizures are occurring, Heminevrin 0.8% should be started at an infusion rate of 5-10ml/min until the fits stop. Once this is achieved the infusion rate is decreased to 0.5-1ml/min, though this may be varied to suit the individual patient, who should be well sedated but communicative.
If the patient is not having a fit at the start of treatment then Heminevrin is given at 3-5ml/min until deep sedation occurs. Once the desired level of sedation is achieved this is maintained with an infusion rate of 0.5 to 1.0ml/min, though this may be varied to suit the individual patient.
The patient should be lying on one side and adequate oxygenation assured. Loss of the airway, pulmonary aspiration of gastric contents, ventilatory failure and circulatory collapse may occur unless the patient is constantly monitored by experienced staff with oxygen and resuscitation equipment available.

Acute Alcohol Withdrawal Symptoms; including delirium tremens
Most patients can be treated with oral Heminevrin but in severe cases an i.v. infusion will give rapid control. The dosing principles mentioned previously, that is, a loading dose for a short period of time followed by maintenance infusion should be used. The initial drip rate should be set in the range of 3 to 7.5ml/min until shallow sleep is induced from which the patient can easily be awakened. Thereafter, the drip rate should be reduced to a maintenance level, usually 0.5 to 1.0ml/min, to achieve the lowest possible rate to maintain shallow sleep and adequate spontaneous breathing.
The patients should be nursed on their side to prevent airway obstruction and turned every 2 hours.
For those patients who urgently require deep sedation, an alternative is to give intravenously 40-100ml of the 0.8% solution over a period of 3-5 minutes. Such treatment should only be given under direct medical supervision. Thereafter maintenance therapy can be established as indicated above.
Because there is a risk of producing unconsciousness with too high a rate of infusion, special attention should be paid to PRECAUTIONS regarding intravenous administration.

Intravenous administration is usually carried out over a period of 6 to 12 hours during which time usually 500 to 1000ml of the 0.8% infusion is given. The level of consciousness and the effect of therapy on symptoms should be checked by interrupting the drip low at intervals. The level of consciousness should lighten rapidly on stopping the drip flow but the longer the administration lasts, the longer the recovery will take. It is desirable to limit the period of intravenous use and to transfer as soon as possible. During prolonged intravenous administration careful attention should be paid to fluid balance and nutrition.

Elderly
Caution is advised as there may be delayed elimination of Clomethiazole.

4.3 Contraindications

Known sensitivity to Clomethiazole. Acute pulmonary insufficiency.

4.4 Special warnings and precautions for use

Heminevrin should be used cautiously in patients with chronic pulmonary insufficiency because there is a risk of respiratory depression.
Heminevrin 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.
The patient should be kept under close and constant observation by a nurse during the period of continuous infusion. With too high a rate of infusion the sleep induced with Heminevrin can pass unnoticed into deep unconsciousness with the consequent risk of mechanical airway obstruction. With overdosage there is always the possibility of causing centrally induced respiratory depression and circulatory collapse.
Because of the possible danger of mechanical airway obstruction occurring in deep sedation during Heminevrin therapy, the patient's airway may be maintained where necessary by the use of an oral airway tube. In addition, facilities for intubation and resuscitation equipment should always be close at hand.
Hypoxia resulting from for example, respiratory insufficiency can manifest itself as an acute confusion state. Recognition and specific treatment of the cause is essential in such patients and other sedative/hypnotics should be avoided.
Moderate liver disorders associated with alcoholism do not preclude the use of Clomethiazole, but 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 the liver coma.
Caution should be observed in patients with chronic renal disease.
Paradoxical worsening may occur in the Lennox Gastaut Syndrome.
Nasopharyngeal/bronchial secretion may be increased at a time when the heavily sedated patient may be unable to cough or maintain the airway.

Patients receiving high doses of Heminevrin in hospital for management of alcohol withdrawal should not be continued on the regime after discharge. The combination of alcohol with high doses of drug may prove fatal.
There has been a report of thrombophlebitis, fever and headache in young children during prolonged Heminevrin infusion. This may have been due to interaction with plastic i.v. cannulae. For administration in small children a motor driven glass syringe should be used in preference to a drip set. A teflon intravenous cannula should be used which can be connected to the syringe by a polythene extension tube. If an infusion set is used it should be changed at least every 24 hours.
As Heminevrin is absorbed by PVC giving sets, there may be some loss in concentration before the drug reaches the patient. Dosage must therefore be adjusted to the patient's response and not given on a fixed milligram basis.
When i.v. Heminevrin is given for longer than 24 hours, there is a possibility of electrolyte imbalance due to the water load involved with the glucose vehicle. Electrolytes such as Na^{+}, K^{+}, Ca^{++} and Cl^{-} can be added to the infusion bottle to produce physiological concentrations. They will not affect the stability of Clomethiazole over a 24 hour period. Other drugs however, must not be added.

4.5 Interaction with other medicinal products and other forms of interaction

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.
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.

4.6 Pregnancy and lactation

Do not use in pregnancy especially during the first trimester, 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.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The most common side-effect appears to be a tingling sensation in the nose and sneezing occurring immediately after the start of the intravenous infusion. Conjunctival irritation has also been noted in some cases. Occasionally these symptoms may be severe and may be associated with severe headache. Increased nasopharyngeal/bronchial secretions can occur in short term use. Rash and urticaria have also been reported. In rare cases anaphylactic reactions have occurred.
Intravenous administration of Heminevrin solution may be followed by moderate tachycardia and a slight but temporary decrease in blood pressure, which is less pronounced the slower the infusion is given. Rapid infusion may cause transient apnoea and hypotension. Care is needed in patients in whom these events may cause cerebral or cardiac complication e.g. elderly.
Thrombophlebitis may occur at the site of injection with intravenous infusion. Neither heparin nor cortisone has been shown to be helpful in preventing such reactions.

4.9 Overdose

Overdosage can produce unconsciousness with deep coma accompanied by respiratory and cardiovascular depression similar to that seen with barbiturate overdosage. Treatment consists of securing the airway, giving oxygen (with assisted or controlled ventilation if necessary) and supporting the circulation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clomethiazole is pharmacologically distinct from both the benzodiazepines and the barbiturates.
Clomethiazole is a short acting hypnotic and sedative with anticonvulsant effects used for the treatment of: pre-eclamptic toxaemia, eclampsia, acute alcohol withdrawal symptoms where oral administration is not practical.

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 with a $t_{1/2}$ of about 5 hours. 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

Dextrose monohydrate
Sodium hydroxide
Water for injection

6.2 Incompatibilities

There may be an interaction with plastic i.v. infusion sets and silastic i.v. cannulae. For administration in small children a motor driven glass syringe should be used in preference to a drip set. A teflon intravenous cannula should be used which can be connected to the syringe by a polythene extension tube. If an infusion set is used it should be changed at least every 24 hours.

As Heminevrin is sorbed by PVC giving sets, there may be some loss in concentration before the drug reaches the patient. Dosage must therefore be adjusted to the patient's response and not given on a fixed milligram basis.

This medicinal product must not be mixed with other medicinal products, except those mentioned in 6.6.

6.3 Shelf Life

30 months.

6.4 Special precautions for storage

Store at 2-8°C (refrigerate). Do not freeze.

6.5 Nature and contents of container

500 ml type II neutral glass infusion bottle, with rubber stopper (chlorobutyl or brombutyl) cap.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Heminevrin 0.8% infusion contains no preservatives and once the sterility seal of the bottle has been broken the solution should be used within 24 hours.

Electrolytes such as Na^+, K^+, Ca^{2+} and Cl^- can be added to the infusion bottle to produce physiological concentrations. They will not affect the stability of Clomethiazole over a 24 hour period.

See also section 4.4.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
600 Capability Green
Luton LU1 3LU
United Kingdom

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