Dosage and Administration
The safety and efficacy of HALFAN in the treatment of patients with cerebral malaria and other forms of complicated malaria have not been established.
Adults and children of more than 40 kg: a total of six tablets (1500 mg) per day given as two tablets at six-hourly intervals.
Children of less than 40 kg: the usual dosage is 24 mg/kg per day divided into three doses given at six hourly intervals, according to the following scheme:

<table>
<thead>
<tr>
<th>Weight Kg</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-12</td>
<td>1 x 5 ml dose of suspension every 6 hours to a total of 3 doses</td>
</tr>
<tr>
<td>13-18</td>
<td>1 x 7.5 ml dose of suspension every 6 hours to a total of 3 doses</td>
</tr>
<tr>
<td>19-25</td>
<td>1 x 10 ml dose of suspension every 6 hours to a total of 3 doses</td>
</tr>
<tr>
<td>26-31</td>
<td>1 x 250 mg tablet dose every 6 hours to a total of 3 doses</td>
</tr>
<tr>
<td>32-40</td>
<td>1.5 x 250 mg tablet dose every 6 hours to a total of 3 doses</td>
</tr>
</tbody>
</table>

The absorption of halofantrine is increased approximately six-fold when taken with a fatty meal.
Therefore, HALFAN should be given on an empty stomach, and fatty foods avoided 24 hours thereafter.

In cases where the patient has no previous exposure to malaria (i.e. travellers from non-endemic areas) or minimal exposure (i.e. young children), a second course of therapy is recommended one week after the first course.

Elderly: No specific dosage recommendations.

Contraindications
HALFAN is contra-indicated in patients with a known history of hypersensitivity (such as immune haemolytic anaemia) to halofantrine or with a known history of congenital QTc prolongation.

Warnings and Precautions
HALFAN has been shown to produce a dose-related...
halofantrine was decreased (See Special Warnings and Precautions).

Pregnancy and Lactation
HALFAN should not be used in pregnant or lactating women unless the potential benefit outweighs the potential risk to the mother, foetus, or newborn. No teratogenic effects were reported from animal studies but developmental toxicity, expressed as an increased frequency of post-implantation embryonic death and reduced foetal body weight, was observed at doses in excess of 15 mg/kg. Data from lactating rats suggest that halofantrine may be secreted in milk because of reduced weight gain in the offspring.

Effects on Ability to Drive and Use Machines
There is no evidence that halofantrine will affect the ability of a patient to drive or use machines.

Adverse Reactions
Data from clinical studies were used to determine the frequency of very common to uncommon undesirable reactions. The frequencies assigned to all other undesirable reactions (i.e. those occurring at <1/1000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.

The following convention has been used for the classification of frequency:
- very common: ≥1 in 10
- common: ≥1 in 100 and <1 in 10
- uncommon: ≥1 in 1,000 and <1 in 100
- rare: ≥1 in 10,000 and <1 in 1,000
- very rare: <1/10,000.

Blood and lymphatic system disorders
Very rare: Immune haemolytic anaemia (which may be severe) which may compromise renal function

Cardiac disorders
Very common: Prolongation of QTc interval
Very rare: Ventricular dysrhythmia very rarely associated with sudden death

These cases have occurred particularly under certain conditions which include the use of doses higher than...
recommended, recent or concomitant treatment with mefloquine, or the presence of pre-existing prolonga-
tion of QTc interval.

**Gastrointestinal disorders**
Very common: abdominal pain, diarrhoea, nausea

**Hepatobiliary disorders**
Very common: Elevated serum Transaminases. Values have returned to normal usually within one week after treatment

**Nervous system disorders**
Very rare: Convulsion (in some cases a cardiac cause was present).

**Skin and subcutaneous tissue disorders**
Very common: pruritus
Common: rash

**Overdose**
There is no experience of acute overdosage with halofantrine. This precludes characterisation of sequelae and assessment of antidotal efficacy at this time. However, in case of accidental overdosage, immediate induction of emesis or gastric lavage is recommended, in conjunction with appropriate supportive measures, which should include ECG monitoring.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamics**

**Mechanism of Action**
Halofantrine is schizontocidal and exerts its action at the erythrocytic stage of the life cycle (trophozoite and schizont). It is not effective against exo-erythrocytic (hepatic) schizonts or against the sporozoite, merozoite or gametocyte stages of the life cycle of Plasmodium species investigated.

**Pharmacodynamic Effects**
It has been demonstrated by in vitro and in vivo animal studies and in man that halofantrine is efficacious in the treatment of P. falciparum and P. vivax infections. Efficacy in a limited number of P. malariae and P. ovale infections has been demonstrated. The majority of patients who have been treated with halofantrine have been infected with P. falciparum in areas of the world where chloroquine or multi-drug resistant strains are common.

**Pharmacokinetics**

**Absorption**
The blood profile and area under the curve (AUC) indicate that halofantrine appears in the systemic circulation within one hour of administration and that the absorption continues at a relatively low rate for several hours. The absorption of halofantrine hydrochloride is known to be variable following single doses (250 to 2000 mg) in healthy subjects, hence the rationale for divided dosing to ensure adequate blood concentrations. The relative bioavailability of halofantrine is increased approximately six-fold when taken with a fatty meal (see Dosage and Administration). This should not be used as a method for enhancing absorption.

**Distribution**
After administration of single doses of halofantrine hydrochloride, plasma levels of halofantrine reach maximum concentration at approximately 6 h after dosing, while those of the equipotent metabolite desbutyl halofantrine occur somewhat later, usually between 10 and 18 h post-dose. The maximum concentration of halofantrine after a single dose of 500 mg averages about 270 nanomol/l (135 nanograms/ml) and concentrations of the metabolite reach about one half this level.

**Metabolism**
In vitro metabolism studies with human liver microsomes indicate that halofantrine is metabolized to its principle metabolite, desalkylhalofantrine, predominately by a specific cytochrome P-450 isozyme, CYP 3A4. Thus, concurrent administration of halofantrine with CYP 3A4 inhibitors may result in significantly increased plasma concentrations of halofantrine.

**Elimination**
The elimination half-life of halofantrine from blood varies with the individual but is generally 24 to 48 h. The desbutyl metabolite has a half life of about twice the parent compound.
The major route of elimination from the body is via the faeces.

**Clinical Studies**
No text

**Pre-clinical Safety Data**
Refer to Pregnancy and Lactation Section.

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**
HALFAN Tablets: Pre gelatinised Starch (Maize), Povidone K30 (Polyvidone) Sodium starch Glycollate, Microcrystalline Cellulose, Talc, Magnesium Stearate
HALFAN Suspension: Microcrystalline cellulose and Sodium carboxymethyl cellulose (eg. Avicel CL 611), Propylene Glycol, Sorbitol liquid (Non-crystallising), Citric Acid, Anhydrous, Sodium Citrate, Sodium Benzoate, Banana-Vanilla Flavour, Silicone Antifoam Emulsion AF9010, Purified Water

**Incompatibilities**
Not applicable

**Shelf Life**
The expiry date is indicated on the packaging.

**Special Precautions for Storage**
Protect tablets and suspension from light.

**Nature and Contents of Container**
Not applicable

**Instructions for Use/Handling**
HALFAN Tablets 250 mg: No special handling instructions.
HALFAN Suspension 2% w/v: Any opened bottle must be used within 15 days. Protect from light.
Not all presentations are available in every country.
Version number: GDS18/IPI03
Date of issue: 24 February 2005
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