Core Safety Profile

Active substance: Halofantrine
Pharmaceutical form(s)/strength: 6x 250 mg tablets; 30 mL of 2% suspension (100 mg/5 mL)
P-RMS: PT/H/PSUR/0007/002
Date of FAR: 09.04.2013
4.3 Contraindications

- Congenital or acquired QTc prolongation
- Familial history of congenital QTc prolongation
- Previous history or current cardiopathy, bradycardia or arrhythmia
- Previous history of syncope
- Hypersensitivity to halofantrine or constituents
- Previous history of blackwater fever with halofantrine, quinine or mefloquine

4.4 Special warnings and precautions for use

Risk of ventricular dysrhythmias
Halofantrine has been shown to produce a dose-related prolongation of the QTc interval, which usually is reversible within 3 to 4 days. This effect has been associated with serious arrhythmias (sometimes with a fatal outcome), even at the recommended therapeutic dose. Halofantrine should be avoided in patients having clinical conditions or receiving drugs known to prolong the QTc interval, in patients with previous history of unexplained syncopes. Therefore, physicians should take a careful history and it is recommended that an ECG is performed prior to commencing treatment with halofantrine to exclude high risk patients (see section 4.3 and 4.5), as halofantrine is contraindicated in patients with known QTc prolongation and not recommended in patients:
- receiving drugs or having clinical conditions known to prolong the QTc interval (see section 4.5)
- with ventricular dysrhythmias, A-V conduction disorders, or unexplained syncopal attacks.

Precautions for use
Halofantrine has been shown to produce a dose-related prolongation of the QTc interval. Caution should be taken to avoid increased blood levels that may be associated with higher than recommended doses, concomitant intake of drugs which are known to significantly inhibit cytochrome p450 3A4 (see section 4.5) or increased absorption with fatty foods. It is essential to:
- take the recommended dose on an empty stomach
- avoid fatty food for 24 hours.

This drug should not be associated with protease inhibitors, azole fungicides, some macrolides, with drugs known to cause torsades de pointes and stiripentol. Precautions specific to second course of therapy:
Halofantrine associated with mefloquine can potentiate cardiotoxicity. Risks of QTc prolongation with quinine should be taken into account. Administration of a second course of therapy to malaria-naïve patients to reduce the risk of relapse may increase plasma levels of the drug which is associated with QTc prolongation and cardiac arrhythmias, therefore additional caution must be taken. Performance of an ECG prior to this course may be advisable. Additionally, the patient must be advised to take the dose on an empty stomach and thereafter to avoid fatty food for 24 hours. This advice is particularly important during a second course of treatment (see section 4.2) as the patient is likely to have improved and be eating normally.

Suspension:
Halofantrine suspension contains sodium benzoate which is a mild irritant to the skin, eyes and mucous membrane. It may increase the risk of jaundice in newborn babies.
4.5 Interactions with other medicinal products and other forms of interaction

**Drugs that can cause torsades de pointe:** antiarrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide), antiarrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide), some neuroleptics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, amisulpride, tiapride, pimozide, haloperidol, droperidol, sultopride), antiparasitics (lumefantrine, pentamidine), bepridil, cisapride, diphemanil, erythromycin IV, methadone, mizolastine, veralipride, vincamine IV.

An interaction with mefloquine has been reported to lead to further prolongation of the QTc interval.

Increased risk of ventricular dysrhythmias, especially torsades de pointes. Not infectious torsadogen drug should be stopped, but if it’s not possible, QTc interval should be controlled before treatment and ECG should be monitored during treatment.

**Erythromycin, clarithromycin, josamycin:** increased risk of ventricular dysrhythmias, especially torsades de pointes. Macrolide should be stopped, but if it’s not possible, QTc interval should be controlled before treatment and ECG should be monitored during treatment.

**Stiripentol:** increased risk of ventricular dysrhythmias, especially torsades de pointes.

**Beta blockers in heart failure** (bisoprolol, carvedilol, metoprolol, nebivolol): increased risk of ventricular dysrhythmias, especially torsades de pointes. Clinical, biological and electrocardiographic monitoring is recommended.

**Bradycardic drugs** (beta-blockers, some calcium channel-blocking agent, anticholinesterasic drugs): increased risk of ventricular dysrhythmias, especially torsades de pointes. Clinical, biological and electrocardiographic monitoring is recommended.

**Hypokaliemic drugs** (hypokaliemic diuretics, stimulating laxatives, amphotericin B (IV route), glucocorticoids, tetracosactid): increased risk of ventricular dysrhythmias, especially torsades de pointes. Clinical, biological and electrocardiographic monitoring is recommended.

In vitro studies have shown that drugs which inhibit cytochrome CYP3A4, e.g. ketoconazole, lead to an inhibition of halofantrine metabolism. Further, in dogs orally administered ketoconazole, the metabolism of halofantrine was decreased (see section 4.4).

**Protease inhibitors** (amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir): increased risk of ventricular dysrhythmias, especially torsades de pointes.

**Azole antifungals** (itraconazole, ketoconazole, fluconazole, miconazole, voriconazole) (systemic route and buccal gel): increased risk of ventricular dysrhythmias, especially torsades de pointes.

4.6 Fertility, Pregnancy and Lactation

Halofantrine 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 in the rat at doses in excess of 15 mg/kg.

Adequate human data during lactation are not available, and animal studies have shown adverse effects on lactation or the breast-fed offspring.

4.7 Ability to perform tasks that require judgement, motor or cognitive skills

There is no evidence that halofantrine will affect the ability of a patient to drive or use machines.
4.8 Undesirable effects

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:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥1/100 to &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥ 1/1000 to &lt; 1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥ 1/10,000 to&lt; 1/1000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt; 1/10,000</td>
</tr>
</tbody>
</table>

Blood and lymphatic system disorders

Very rare: Immune haemolytic anaemia (which may be severe) which may compromise renal function. Some of these anaemia occurred after the first intake of halofantrine. The mechanism is not clearly evidenced but an immunoallergic reaction is considered.

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 prolongation 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

Immune system disorders

Common: Urticaria
Very rare: Anaphylactic shock
4.9 Overdose

Symptoms and Signs
There is no experience of acute overdosage with halofantrine. This precludes characterisation of sequelae and assessment of antidotal efficacy at this time. A potential risk of QTc prolongation associated with serious ventricular dysrhythmias, especially torsades de pointes, exists. In case of accidental overdosage, immediate management, which should include ECG monitoring, is required and this should be as clinically indicated, or as recommended by the national poisons centre, where available.