Core Safety Profile

Active substance: Hydroquinidine
Pharmaceutical form(s)/strength: Delayed release capsule, 300mg
P-RMS: ES/H/PSUR/0004/001
Date of FAR: 09.03.2012
Core Safety Profile – [HYDROQUINIDINE HYDROCHLORIDE]

Formulations:

4.3 Contraindications

Hydroquinidine hydrochloride MUST NEVER BE USED in the following situations:
- hypersensitivity to hydroquinidine or quinidine (cf. Section 4.4 Warnings and precaution for use).
- unpaced atrio-ventricular block.
- complete bundle-branch block, other significant intraventricular conduction disorders.
- Disorders of sinus node automaticity (sick sinus syndrome) unless a pacemaker is fitted.
- rhythm disorders due to digoxin intoxication
- torsades de pointe.
- prolonged QT interval.
- cardiac insufficiency.
- association with beta blockers indicated in the treatment of cardiac insufficiency : bisoprolol, carvedilol, metoprolol
- association with medicaments which could induce torsades de pointe:
  - class Ia anti-arrhythmic (quinidine, disopyramide).
  - class III anti-arrhythmic (amiodarone, sotalol, dofetilide, ibutilide, etc.)
  - sulthiamide (neuroleptics)
  - and other drugs such as: bepridil, disapride, diphemanil, erythromycin IV, mizolastine, spiramycin IV, vincamycin IV (cf. Section 4.5, Interactions with other medicaments and other forms of interactions).

4.4 Special warnings and precautions for use

Warnings

Other class I anti-arrhythmics have been tested in a double blind randomised multi-centred trial (CAST trial) in asymptomatic, non life-threatening ventricular dysrhythmias in people more than 6 days and less than 2 years after a myocardial infarction. The incidence of death and non-fatal cardiac arrest associated with these medicinal products was higher than in the placebo group.
As for the other class I anti-arrhythmic agents, no controlled trials have demonstrated beneficial effects of hydroquinidine in terms of survival or sudden death.

**Idiosyncratic hypersensitivity**

Because of the possible development of extremely severe hypersensitivity reactions (particularly sudden cardiocirculatory arrest) patients must be tested for sensitivity to hydroquinidine before treatment initiation.

- A single capsule test is administered
- If a patient develops hypotension, skin rash, an episode of fever, asthmatic attack or prolonged QT interval by 0.04 seconds or more or in case of enlarged QRS more than 25% and (or) in case of multiformal extrasystoles during the first hours after the first dose: the treatment must be stopped.
- Conversely, if electrocardiographic changes only occur after 48 hours (and in the absence of the other signs described above) it is sufficient to reduce the doses.
- Hydroquinidine may induce torsades de pointe. The serum potassium must be monitored (hypokalaemia predisposes to this severe ventricular dysrhythmia which is responsible for syncope and sudden death) and patients monitored by regular ECGs, particularly when treatment is started for changes in the length of the QT interval.
- A liver profile should be performed if unexplained fever develops.

As it contains saccharose, this medicinal product is contra-indicated in cases of fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency.

**Special precautions for use**

**Pro-arrhythmic effects**

Like the other anti-arrhythmic agents, hydroquinidine may cause the development of a more severe form of arrhythmia, an increase in the frequency of pre-existing arrhythmia or a worsening of the severity of symptoms. Spontaneous variations in the dysrhythmia specific to the patient may be difficult to distinguish from secondary worsening on administration of this medicinal product. This treatment must be stopped if more frequent or polymorphic ventricular extrasystoles develop.

**Electrocardiographical changes**

- Hydroquinidine must be administered with caution in patients with pre-existing conduction abnormalities.
- Hydroquinidine must be stopped if atrio-ventricular block, permanent bundle branch block or sino-atrial block occur on treatment.
- The dosage should be reduced if the QRS complex broadens by more than 25%.
- The medicinal product should be stopped if the QT interval is prolonged by more than 25%.

Patients (particularly those with conduction abnormalities) should be closely monitored by electrocardiograms if the dosage of hydroquinidine or associated treatments are changed, which may affect cardiac conduction.

**Electrolyte disturbances**
Hypokalemia or hypomagnesaemia may provoke the pro-arrhythmic effects of class I anti-arrhythmics and must be corrected before administering hydroquinidine hydrochloride.

Renal insufficiency
Electrolyte monitoring must be increased (hyperkalemia increases the effects of hydroquinidine). If needed the dosage should be adjusted as a function of plasma concentrations.

Patients with cardiac pacemakers
Be aware of a possible rise in the pacing threshold.

Hydroquinidine hydrochloride IS GENERALLY NOT RECOMMENDED in the following situations:
- pregnancy, breast-feeding,
- myasthenia,
- in association with:
  - halofantrine
  - pentamidine
  - moxifloxacin
  - certain neuroleptic agents (thioridazine, chloropromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, amisulpride, tiapride, pimozone, haloperidol, droperidol).
  (cf. Section 4.5 Interactions with other medicaments and other forms of interaction).

4.5 Interaction with other medicinal products and other forms of interaction

Many anti-arrhythmics depress cardiac automaticity, conduction and contractility.
Association of different classes of anti-arrhythmics may produce a beneficial therapeutic effect but usually requires great care and close clinical and ECG monitoring.
Association of anti-arrhythmics that induces torsades de pointe (amiodarone, disopyramide, quinidine derivatives, sotalol) is CONTRA-INDICATED.

The association of same class of anti-arrhythmics is RECOMMENDED AGAINST except in exceptional cases, because of the increased risk of undesirable cardiac effects.
Association with medicinal products which have pro-bradycardic and negative inotropic effects and/or slow atrio-ventricular conduction should be used with care and requires clinical and ECG monitoring.

Associations contra indicated
Medicaments inducing torsades de pointe: class I anti-arrhythmics (quinidine, disopyramide etc), class III anti-arrhythmics (amiodarone, sotalol, dofetilide, ibutilide, etc), sultopride (neuroleptic), bepridil, cisapride, diphemanil, erythromycin IV, mixolastine, spiramycin IV, vinamine IV, etc.
Increased risk of ventricular disorders, particularly torsades de pointe.
Beta blockers indicated in treatment of cardiac insufficiency (bisoprolol, carvedilol and metoprolol).

Negative inotropic effect with risk of decompensating cardiac insufficiency (synergistic activities).

**Not recommended Associations**

Some neuroleptic agents (thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, amisulpride, tiapride, haloperidol, pimozide, droperidol, etc.).

Increased risk of ventricular arrhythmias, particularly torsades de pointe.

**Halofantrine, pentamidine, moxifloxacin**

Increased risk of ventricular dysrhythmias, particularly torsades de pointe.

Where possible, discontinue the non anti-infectious medicinal product which produces torsades de pointe.

If the association cannot be avoided check the QT interval first and monitor by electrocardiogram.

**Associations requiring precautions for use**

**Urine alkalinising agents: acetazolamide, sodium bicarbonate, trometamol**

Increase in plasma hydroquinidine concentrations and risk of overdose (reduced renal excretion of hydroquinidine caused by alkalanisation of urine).

Clinical and ECG monitoring, possible monitoring of plasma anti-arrhythmic concentrations. If necessary adjust dosage of hydroquinidine during and after stopping alkalanising treatments.

**Anti-cholinesterase agents (donepezil, rivastigmine, tacrine, galantamine, neostigmine, pyridostigmine, ambenonium)**

Risk of excessive bradycardia (additive pro-bradycardic effects).

Regular clinical monitoring.

**Beta blockers (except sotalol, bisoprodol, carvedilol and metoprolol)**

Disorders of contractility, automaticity and conduction (abolition of compensating sympathetic mechanisms).

Clinical and ECG monitoring.

**Pro-bradycardic agent (pro-bradycardic calcium antagonists: diltiazem, verapamil; beta blockers: clonidine, guanfacin, digoxin and related compounds, mefloquine, anti-cholinesterases particularly those used in Alzheimer’s disease)**

Increased risk of ventricular dysrhythmias, particularly torsades de pointe.

Clinical and electrocardiographical monitoring.

**Digoxin (and by extrapolation, deslanoside)**

Increase in plasma digoxin concentration due to a fall in renal digoxin clearance. Additionally, disorders of automaticity (excessive bradycardia and atrio-ventricular conduction disorders).

Clinical and ECG monitoring. If an unexpected response is seen, measure blood digoxin concentration and adjust dosage.
Agents producing hypokalemia (diuretics producing hypokalaemia (alone or in association), stimulant laxatives, amphotericin B (IV route), glucocorticoids (systemic route), tetracosactide).

Increased risk of ventricular dysrhythmias, particularly torsades de pointe.
Correct any hypokalemia before administering the substance and monitor clinically and by electrolyte and electrocardiography.

Enzyme inducers (anticonvulsants: carbamazepine, phenobarbital, phenytoin, primidone, rifampicin).

Reduction in plasma concentrations and efficacy of hydroquinidine due to an increase in its hepatic metabolism.
Clinical and ECG monitoring and where applicable measurement of plasma hydroquinidine concentrations. If necessary, adjust the dosage of the anti-arrhythmic during and after stopping treatment with the enzyme inducer.

Itraconazole
Risk of tinnitus and/or reduction in auditory acuity: cinchonism due to reduced hepatic metabolism of hydroquinidine caused by itraconazole.
Monitor plasma concentrations of hydroquinidine and where applicable reduce dosage.

4.6 Fertility, pregnancy and lactation

Pregnancy
No reliable teratogenesis data exist in animals.
At present there are insufficient pertinent clinical data to evaluate any pro-malformation or foetotoxic effects of hydroquinidine when administered during pregnancy.
As a consequence, use of hydroquinidine is not recommended during pregnancy.

Lactation
As hydroquinidine passes into breast milk and produces secondary effects, breast-feeding should be avoided during treatment with hydroquinidine.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Frequencies were defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).
<table>
<thead>
<tr>
<th>Disorder Type</th>
<th>Very Common</th>
<th>Common</th>
<th>Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>thrombocytopenic purpura, haemolytic anaemia.</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Cases of hypersensitivity</td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td>dizziness</td>
<td>diplopia, photophobia, ringing in the ears</td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
<td>hypoacousis</td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td>cardia arrhythmia and conduction disorders, cardiac arrest, atrioventricular block, intraventricular block, extra-systoles, ventricular fibrillation, torsades de pointe,</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>diarrhoea</td>
<td>nausea</td>
<td>vomiting</td>
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<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td>cases of immuno-allergic hepatic disease usually accompanied by fever</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td></td>
<td></td>
<td>photosensitivity reaction</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
<td>cinchonism (mostly in cases of overdose) see section overdose</td>
</tr>
</tbody>
</table>

4.9 Overdose

The symptoms of overdose are seen at massive doses (equivalent to 4 g of hydroquinidine base or more). The symptoms are: gastro-intestinal and neurosensory (visual, auditory), respiratory (apnoea) problems, agitation, hypotension.

The ECG appearances range from bundle branch block or bifascicular block, and QRS complex broadening to major ventricular arrhythmias: ventricular tachycardia, torsades de pointe, ventricular fibrillation).