Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mexitil Ampoules 25mg/ml Solution for Injection and Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 25 mg/ml mexiletine hydrochloride.
One 10 ml ampoule contains 250 mg mexiletine hydrochloride.
Also contains 0.75mg (33mmol) Sodium per ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection and infusion
Clear, colourless or almost colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of ventricular arrhythmias which are considered as life-threatening by the physician.

Note:
In deciding about the use of Mexitil it should be borne in mind that no anti-arrhythmic agents of Vaughan Williams classification 1 including mexiletine used in the long-term treatment of arrhythmias has been shown to prolong life.

4.2 Posology and method of administration

Plasma elimination half-life may be prolonged in moderate to severe hepatic disease, and in patients with creatinine clearance of less than 10 ml/min: individual dose titration is advised in these conditions.

1 Intravenous Mexitil
Mexitil should never be injected in bolus form.

(a) Loading Dose
IV injection of 4 – 10 ml (100 – 250 mg) Mexitil given at a suggested rate of 1 ml per minute (25 mg per minute). THEN Add 500 mg (2 ampoules) Mexitil to 500 ml of a suitable infusion solution. Administer the first 250 ml by IV infusion over 1 hour (4 ml per minute). THEN Administer the second 250 ml by IV infusion over 2 hours (2 ml per minute).

(b) Maintenance Dose
Add 250 mg (1 ampoule) Mexitil to 500 ml of suitable infusion solution. Administer at a suggested rate of 1 ml per minute (0.5 mg per minute), according to patient response. Continue for as long as required or until oral maintenance therapy is commenced.

2 Alternative Loading Dose Regimes
(a) Combination IV Mexitil and Oral Mexitil Loading Dose
IV injection of 8 ml (200 mg) Mexitil given at a suggested rate of 1 ml per minute. On completion of injection or infusion give 400 mg Mexitil orally.

(b) Maintenance Dose
As in 1(b) above.

3 Change over from IV to Oral Mexitil Maintenance
On discontinuing the IV infusion, commence the maintenance dose. The first capsule should be taken at, or shortly before, the end of the infusion. (An oral loading dose should not be given).

Notes:

1 The loading dose regime is designed to compensate for the rapid phase of tissue distribution, which occurs especially with IV loading.

2 Side-effects are more likely to be encountered during the initial tissue loading phase, in which case the rate of infusion should be reduced.

3 If the optimum therapeutic affect is not achieved, the rate of infusion or oral dosage may be increased, side-effects permitting.

4 When mexiletine therapy is commenced, patients should be monitored closely (e.g. ECG, blood pressure and routine laboratory tests) over a period of at least 24 hours, and dosage adjustment made on the basis of this. Monitoring is particularly recommended in the following situations: sinus node dysfunction, conduction defects, bradycardia, hypotension or cardiac, renal or hepatic failure. There may be potentiation of tremor in patients with Parkinsonism.

Regular monitoring of cardiac function throughout treatment is advisable.

The duration of treatment required in any patient is variable, and although no precise guide can be given, withdrawal may be attempted after a suitable period free of arrhythmia. Gradual withdrawal i.e. over 1- 2 weeks, is preferable as arrhythmias which have been satisfactorily controlled may recur. No specific information on the use of this product in the elderly or children is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

Mexitil solution for injection is known to be compatible with the following infusion solutions: sodium chloride 0.9 %, sodium chloride 0.9 % with potassium chloride 0.3 % or 0.6 %, dextrose 5 %, sodium bicarbonate, sodium lactate (M/6).

Diluted Mexitil should not be stored for longer than 8 hours.

4.3 Contraindications

Mexitil should not be used in the first three months following myocardial infarction or where cardiac output is limited (left ventricular ejection fraction of less than 35 %), except in patients with life-threatening ventricular arrhythmias.

Mexitil is contraindicated in the presence of cardiogenic shock or pre-existing second- or third- degree AV block if no pacemaker is present.

Hypersensitivity to mexiletine or local anaesthetics e.g. lidocaine (lignocaine).

4.4 Special warnings and precautions for use

i. If the drug is used in the following situations, the patient should be carefully monitored and the dosage may need to be reduced: sinus node dysfunction, conduction defect, bradycardia, hypotension or cardiac failure.

ii. Plasma elimination half-life may be prolonged in moderate to severe hepatic disease, and in patients with creatinine clearance of less than 10 ml/min: individual dose titration is advised in these conditions.

iii. Patients in whom pathologically high liver values have been established or who have signs or symptoms of impaired liver function, should be monitored carefully.

iv. Careful monitoring is also recommended in patients with convulsive disorders.

4.5 Interaction with other medicinal products and other forms of interaction

i Where there is concurrent administration of Mexitil and some other anti-arrhythmic drugs, an increased effect on conduction and contractility of the heart is to be expected. Mexitil may be used concurrently with the cardiovascular drugs digoxin, amiodarone, quinidine and beta-adrenergic blocking agents.

ii Since Mexitil is metabolised mainly in the liver, substances that influence liver enzyme function may alter the concentration of Mexitil in the blood. In particular, interactions with the two cytochrome P450 isozymes CYP1A2 and CYP2D6 have to be considered. It may be necessary to reduce the dose of Mexitil in cases of concomitant administration of substances that lead to enzyme inhibition in the liver.

In cases of concurrent therapy with substances that lead to enzyme induction, it may be necessary to increase the dose of Mexitil since it is metabolised at a faster rate.

iii Concurrent administration of mexiletine may increase plasma levels of theophylline and caffeine.

iv Drugs which markedly acidify or alkalise urine should be avoided because they may enhance or reduce (respectively) the rate of drug excretion, and correspondingly affect the plasma concentration of mexiletine.

v Concomitant administration of Mexitil with warfarin may increase the risk of bleeding.

vi Local anaesthetic toxicity may occur in patients who receive Mexitil and local anaesthetic agents concurrently.

4.6 Pregnancy and lactation

Mexiletine freely crosses the placenta. Therefore, Mexitil should only be used in pregnancy if the potential benefit justifies the potential risk.

Mexiletine appears in breast milk in concentrations which may have an effect on the infant. Therefore, if the use of Mexitil is deemed essential for the mother, an alternative method of infant feeding should be considered.

4.7 Effects on ability to drive and use machines

Mexitil may impair the ability to drive or operate machinery, especially when taken in combination with alcohol.

4.8 Undesirable effects

Side-effects are mainly related to blood concentration and may, therefore be seen during the initial phases of both IV and oral treatment when fluctuation may occur before the blood and tissue concentrations reach equilibrium. Reducing the rate of injection of infusion or delaying the next oral dose allows the blood concentration to fall and usually reduces side-effects.

The most commonly reported side effect of MEXITIL is heartburn, occurring in about 18% of patients.

The following side effects have been reported during use of MEXITIL; note that where frequencies have been assigned these have been based on clinical trials in 651 patients for which all adverse events have been reported on an individual basis. Other adverse events have been reported and are also listed below.

Blood and the lymphatic system disorders

Rare: Leucopenia, neutropenia, agranulocytosis, and thrombocytopenia.

Immune system disorders

Rare: Allergic reactions, lupus-like symptoms.

Psychiatric disorders

Common: Confusion
Uncommon: Somnolence,
Rare: Hallucinations, psychotic disorders, insomnia.

Nervous system disoders

Common: Tremor, dizziness, nystagmus, paraesthesia.
Uncommon: Ataxia, convulsion, speech disorder.

Eye disorders

Common: Abnormal vision e.g. blurred vision, diplopia.

Cardiac disorders

Common: Palpitations.
Uncommon: Arrhythmia, bradycardia.
Rare: Atrial fibrillation, all grades of AV blockade (in isolated cases with syncope), cardiac failure, ventricular arrhythmia, conduction defects, torsades de pointes.

Vascular disorders

Uncommon: Hypotension.

When hypotension has occurred this has tended to be in patients with severe illness who have already been given a variety of anti-arrythmic or other preparations and, if associated with bradycardia, may be reduced by the use of atropine.

Respiratory, thoracic and mediastinal disorders.

Rare: Lung infiltration, pulmonary fibrosis.

Gastro-intestinal disorders

Very common: Heartburn.
Common: Dyspepsia, nausea, vomiting.
Rare: Retching, unpleasant taste, constipation, diarrhoea, dry mouth, hiccoughs.

Hepato-biliary disorders

Rare: Hepatocellular damage, abnormal hepatic function, hepatic necrosis, jaundice has been reported.

Skin and subcutaneous tissue disorders

Uncommon: Rash.
Rare: Erythroderma, Stevens -Johnson syndrome.

General disorders

Rare: Hot flush, fever, Arthralgia.

Investigations

Rare: Antinuclear antibodies positive, liver function test abnormal.

Frequencies:

Very common >1/10
Common>1/100<1/10
Uncommon >1/1000 <1/100
Rare >1/10000 <1/1000
Very rare >1/10000

4.9 Overdose

The minimum fatal dose is unknown but 4.40g proved fatal in a healthy young adult.

The clinical features include nausea, vomiting, drowsiness, confusion, ataxia and convulsions. Blurred vision and paraesthesiae have also been reported. Hypotension, sinus bradycardia, atrial fibrillation and cardiac arrest are more specific effects.

Therapy:
General symptomatic treatment is advisable.

Arrhythmias should be treated as appropriate and intravenous diazepam may be useful to control convulsions. In the event of serious bradycardia and hypotension, it is advisable to first administer an IV dose of 0.5 – 1.0 mg atropine.

Acidification of the urine enhances the rate of drug elimination and so may be useful.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Antiarrhythmics, class IB.
ATC code: CO1B B02.

Mexitil (mexiletine hydrochloride) is a Class 1b anti-arrhythmic agent based on the Vaughan Williams classification with local anaesthetic properties, similar in structure and activity to lidocaine (lignocaine). Mexiletine depresses the maximum rate of depolarisation with little or no modification of resting potentials or the duration of action potentials.

5.2 Pharmacokinetic properties

Mexiletine is metabolised in the liver to a number of metabolites. It is excreted in the urine, mainly in the form of its metabolites with a small proportion of unchanged mexiletine; the clearance of mexiletine is increased in acid urine. Mexiletine is widely distributed throughout the body and is about 50-70 % bound to plasma proteins. It has a plasma half-life of 5-17 hours in healthy subjects but this may be prolonged in patients with heart disease.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injection

6.2 Incompatibilities

This product must not be mixed with any medicinal products other than those listed in section 6.6.

6.3 Shelf Life

5 years. Diluted Mexitil should be discarded after 8 hours.

6.4 Special precautions for storage

Do not store above 25ºC. Keep the ampoules in the outer carton.

6.5 Nature and contents of container

Cartons containing 5 x 10 ml colourless Type I glass ampoules.

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

Mexitil solution for injection is known to be compatible with the following infusion solutions: sodium chloride 0.9 %, sodium chloride 0.9 % with potassium chloride 0.3 % or 0.6 %, dextrose 5 %, sodium bicarbonate, sodium lactate (M/6).

Mexitil Ampoules are for single use only, any unused contents should be discarded.

7 MARKETING AUTHORISATION HOLDER

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Bracknell
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8 MARKETING AUTHORISATION NUMBER

PA 7/1/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 November 1975

Date of last renewal: 13 July 2006

10 DATE OF REVISION OF THE TEXT

December 2006