Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mexitil Capsules 200mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg mexiletine hydrochloride.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsules
Red/red gelatin capsules imprinted with the notation 200 mg and the company symbol.

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 agent of Vaughan Williams classification 1 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 a creatinine clearance of less than 10 ml/min; individual dose titration is advised in these conditions.

The dosage of Mexitil must be individualised on the basis of response and tolerance, both of which are dose related.

(a)Capsules should be swallowed whole with ample liquid, preferably with the patient in an upright position. It is advisable to take Mexitil after food.

*(i) Loading dose:*Initially, if more rapidly effective blood levels are required, a loading dose, usually 400 mg may be desirable.

*(ii)Maintenance dose:*Give 200-250 mg Mexitil three to four times daily commencing 2 hours after the loading dose. The usual daily dose is between 600-800 mg in divided doses; optimal doses range from 300-1200 mg daily in divided doses.

*NOTE:*Mexitil is absorbed in the upper part of the small intestine. In acute myocardial infarction and particularly when opiates have been given, rate of absorption but not bioavailability may be delayed and therefore, a larger loading dose e.g. 600 mg may be preferable.

(b) **Alternative loading dose regimes:**

(i) 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.

Maintenance dose: As in (aii).

(ii) Combination IV lidocaine (lignocaine) and oral Mexitil loading dose: Give IV lidocaine (lignocaine) according to manufacturer's instructions. On completion of injection give 400 mg Mexitil orally.

Maintenance dose: As in (aii).

(c) **Change over from IV to oral 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). Give 200 – 250 mg Mexitil orally three or four times a day.

(d) **Change over from Capsules to Perlongets**
Give the first Perlonget in the evening, in place of the capsule. Alternatively, the first Perlonget may be given together with the last capsule in the morning.

NOTES:

1 The loading dose regime is designed to compensate for the rapid phase of tissue distribution which occurs especially with IV loading.
2 If the optimum therapeutic effect is not achieved, the oral dosage may be increased, side effects permitting.
3 Gastric emptying time may be delayed in patients with myocardial infarction and/or to whom opiates have been given and thus, it may be necessary to titrate the dose against therapeutic effects and side effects.
4 The 50 mg capsule is available in order that a more precise dose titration may be undertaken should this be required. Small increments will also reduce the incidence of side effects.
5 When mexiletine therapy is commenced, patients should be monitored closely (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 a 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 of necessity variable, and although no precise guide can be given, withdrawal of treatment 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.

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.

Mexitil should not be used in known cases of hypersensitivity to mexiletine or one of the excipients of the product, 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. Myocardial infarction results in prolonged absorption half-life of oral mexiletine.

iii. 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.

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

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 pumping 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. All medicines that affect gastrointestinal movement may affect the absorption of oral Mexitil. Drugs that delay gastric-emptying (e.g. opiates, antacids and atropine) may delay the absorption of Mexitil. Similarly, drugs that accelerate gastric-emptying (e.g. metoclopramide) will reduce the time to peak mexiletine concentrations and increase peakconcentrations.

iii. 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.

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

v. 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.

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

vii. 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.

Mexitil 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 or infusion or delaying the next oral dose allows the blood concentration to fall and usually reduces side-effects. Generally side-effects are of five types:

Gastro-Intestinal - Nausea, vomiting, indigestion, constipation, diarrhoea, dry mouth, unpleasant taste, hiccoughs. Oesophageal ulceration may occur if oral Mexitil is swallowed without adequate liquid and is lodged in the oesophagus.

Central Nervous System - Drowsiness, dizziness, diplopia, blurred vision, nystagmus, dysarthria, ataxia, tremor, paraesthesiae, convulsion, psychiatric disorders, confusional state, insomnia.

Cardiovascular - Hypotension, sinus bradycardia, atrial fibrillation, palpitation and conduction defects. Exacerbation of arrhythmias, pre-existing heart failure and torsade de pointes.

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

Pulmonary infiltrates, interstitial lung disease and pulmonary fibrosis have been observed in isolated cases.

Haematological - Rash, arthralgia, fever, thrombocytopenia and appearance of positive but symptomless antinuclear factor titres. Leucopenia has been observed rarely. Rare cases of Stevens-Johnson syndrome, some with liver involvement, have been reported in Japan. Isolated cases of erythroderma have also been reported.

Hepatic - Liver damage has been observed following Mexitil administration; jaundice has been reported.

4.9 Overdose

The minimum fatal dose is unknown but 4.40 g 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. Gastric lavage should be performed where appropriate and the patient should be transferred to an intensive / coronary care unit for possible cardio-pulmonary support.

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

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 primarily absorbed in the upper portion of the small intestine. Peak plasma levels are reached 2-3 hours after administration to normal subjects; absorption is slower after myocardial infarction. Mexiletine shows a fast distribution phase, a slow distribution phase and a slow elimination phase. Tissue up-take is substantial. Bioavailability is about 80 8 %. Renal clearance varies with urine pH but this is unlikely to have clinical significance. In patients the elimination half-life is 5 - 17 hours.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dried Maize Starch
Colloidal Anhydrous Silica
Magnesium Stearate

Capsule shell:

Gelatin
Erythrosine (E127)
Indigo Carmine (E132)
Titanium dioxide (E171)

Printing Ink:

Shellac
Soya lecithin
Dimethicone
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC blister packs (backed with PVC-lacquered aluminium) of 100.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Limited
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RG12 8YS
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8 MARKETING AUTHORISATION NUMBER

PA 7/1/3

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