

# New Zealand Datasheet

## Name of Medicine

MEXITIL®

Mexiletine hydrochloride

## Presentation

*Capsule: 50mg:* red/purple hard gelatine, imprinted with the notation 50mg and the company symbol.

*Capsule: 200mg:* red/red hard gelatine, imprinted with the notation 200mg and the company symbol.

## Uses

### Actions

MEXITIL (mexiletine hydrochloride) is a class 1B anti-arrhythmic agent based on the Vaughan-Williams classification 1 with local anaesthetic properties, similar in structure and activity to lignocaine.

### Pharmacokinetics

Following oral administration, MEXITIL is absorbed rapidly and almost completely from the gastrointestinal tract. In humans, absolute bioavailability following oral administration of aqueous solutions is approximately 88%, for MEXITIL capsules is  $80 \pm 8\%$ .

Delayed absorption has been observed in patients who have suffered an infarction.

On account of its physico-chemical properties as a primary amine with a  $pK_a$  of 8.5 - 9.0 and high lipophilia, the active ingredient is distributed rapidly and widely throughout the body.

Maximum plasma concentrations are reached with oral MEXITIL after 2 - 3 hours. In order to maintain plasma levels which are constantly effective, the interval between doses of MEXITIL should be 6 - 8 hours.

Plasma concentrations of MEXITIL increased proportionally with increasing doses. Higher concentrations are achieved in tissue and breast milk than in plasma.

The therapeutic plasma levels range from about 0.75 µg/ml to 2.0 µg/ml. Half-lives of 5 - 12 hours have been measured for elimination of MEXITIL from the plasma. The values following single intravenous and oral doses are identical.

In the area of therapeutic plasma concentrations, the reversible binding of MEXITIL to plasma proteins is about 55%.

MEXITIL is extensively metabolised in the body. Since approximately 90% of MEXITIL is broken down in the liver into inactive metabolites, pathological changes in the liver can restrict hepatic clearance of MEXITIL and its metabolites. The metabolic degradation proceeds via various pathways including aromatic and aliphatic hydroxylation, dealkylation, deamination and N-oxidation. Several of the resulting metabolites are submitted to further conjugation with glucuronic acid (phase II metabolism), among these are the major metabolites p-hydroxymexiletine, hydroxymethylmexiletine and N-hydroxymexiletine.

Carbamoyl-glucuronidation of MEXITIL is another major metabolic pathway that accounts to approx. 30%.

In man, the absolute bioavailability following oral administration of aqueous solutions was determined at 88%. Values of  $80 \pm 8\%$  were measured for MEXITIL capsules

## **Indications**

Ventricular arrhythmias, if serious in terms of symptoms and/or life threatening in view of the physician.

## **Dosage and Administration**

The dosage of mexiletine must be individualised on the basis of response and tolerance, both of which are dose related. Satisfactory control can be achieved in most patients with a 2 - 3 times daily dose every 8 to 12 hours apart. It is important that MEXITIL capsules be swallowed with ample liquid, preferably with the patient in an upright position. It is advisable to take MEXITIL after food.

Capsules

### Initial dose:

If initially even more rapid effective blood levels are required, a loading dose, usually 400 mg may be desired.

### Maintenance dose:

The first maintenance dose should be given between 2 - 6 hours after the loading dose, depending upon the clinical response.

The usual daily dose is between 400 - 800 mg in divided doses. Some patients may require a maintenance dose of up to 1200 mg daily in divided doses, whereas for other patients a maintenance dose of 300 - 600 mg daily in divided doses may be sufficient.

## **Adjustment of MEXITIL treatment**

In patients with decompensated liver cirrhosis, and in those with severe renal failure, a dose reduction should be considered on an individual basis.

Adjustment of antiarrhythmic treatment in patients suffering from ventricular arrhythmias may only be carried out by monitoring (e.g. ECG, blood pressure) and where the appropriate cardiological emergency equipment is available. It is recommended that this control be carried out over a period of at least 24 hours.

In certain cases an individually adjusted dosage may be necessary. Titration of dosage may be accomplished with lower-dosed MEXITIL capsules where appropriate.

The duration of treatment required in any patient is variable. In view of the severity of the illness and the known possible change of the clinical picture, regular cardiological checks of the patients are advisable.

The patient should be monitored in cases where MEXITIL treatment is to be terminated, since arrhythmias may frequently recur.

## **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 A V block if no pacemaker is present.

MEXITIL should not be used in patients known to be hypersensitive to the active ingredient or one of the excipients of the product, or to local anaesthetics (e.g. lignocaine).

## **Warnings and Precautions**

If MEXITIL is used in the following situations the patient should be closely monitored and dosage reduced if necessary: sinus node dysfunction, conduction defect, bradycardia, hypotension or cardiac failure.

Patients with uncompensated liver cirrhosis show evidence of delayed breakdown and elimination rates of MEXITIL. This may also occur in patients with severe renal failure. In these patients, the dose must be adjusted on an individual basis.

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

Careful monitoring is also recommended in patients with convulsive disorders.

Even if MEXITIL is used as prescribed, it can influence reactions to such an extent that the ability to drive or operate machinery is limited. This applies to an even greater extent in combination with alcohol.

## **Use in Pregnancy and Lactation**

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.

## **Adverse Effects**

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

Oesophageal ulcerations may occur if MEXITIL capsules are swallowed without adequate liquid and become lodged in the oesophagus.

The following side effects have been reported during use of MEXITIL:

Blood and the lymphatic system disorders  
leucopenia, neutropenia, agranulocytosis, and thrombocytopenia

Immune system disorders  
allergic reactions, lupus-like symptoms, drug induced hypersensitivity syndrome, potentially with fatal outcome

Psychiatric disorders  
confusion, somnolence, hallucination, psychotic disorders

Nervous system disorders  
tremor, dizziness, nystagmus, paraesthesia, ataxia, convulsion, speech disorder

Eye disorders

abnormal vision

**Cardiac disorders**

palpitations, arrhythmia, bradycardia, atrial fibrillation, all grades of AV-blockade (in isolated cases with syncope), cardiac failure, ventricular arrhythmia

**Vascular disorders**

hypotension

**Respiratory, thoracic and mediastinal disorders**

lung infiltration, pulmonary fibrosis

**Gastro-intestinal disorders**

heartburn, dyspepsia, nausea, vomiting, oesophageal ulcerations, retching, taste perversion

**Hepato-biliary disorders**

hepatocellular damage, hepatic function abnormal, hepatic necrosis

**Skin and subcutaneous tissue disorders**

rash, erythroderma, Stevens-Johnson-Syndrome

**General disorders**

hot flush

**Investigations**

antinuclear antibodies positive, liver function test abnormal

**Interactions**

Where there is a concurrent administration of MEXITIL and other antiarrhythmic drugs, an increased effect on conduction and contractility of the heart is to be expected. Combinations with propranolol, quinidine and amiodarone have been used.

All medicines which affect gastrointestinal movement may affect the absorption of oral MEXITIL.

Opiates may delay the entry of MEXITIL into the bloodstream.

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 isoenzymes 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. In cases of concurrent therapy with MEXITIL the serum level of theophylline rises. The same applies to caffeine.

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

An increased tendency to bleed has been observed when MEXITIL has been administered to some patients stabilised on Warfarin.

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

## **Overdosage**

### **Symptoms**

Cardiac arrest and convulsions occurred as a result of severe overdosage in addition to symptoms listed under side effects such as nausea, paraesthesiae, drowsiness, confusion, bradycardia and hypotension.

### **Treatment**

General symptomatic and supportive treatment according to the current state of the art is advisable. In the event of convulsions the intravenous administration of diazepam may be indicated.

## **Pharmaceutical Precautions**

Store in a safe place out of reach of children  
Capsules store below 30°C

## **Medicine Classification**

Prescription Medicine.

## **Package Quantities**

Capsule, 50mg and 200mg, 100s.

## **Further Information**

MEXITIL<sup>®</sup> is a registered trademark

## **Excipients**

Maize starch, aerosil 200, magnesium stearate, ethanol absolute denatured, gelatine capsules.

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