SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mexiletine hydrochloride 200 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 200 mg hard capsule contains 200 mg of mexiletine hydrochloride, equivalent to 166.20 mg of mexiletine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard Capsules

Opaque hard gelatin capsules of light blue body and light blue cap (size 1).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mexiletine is indicated for the treatment of documented ventricular arrhythmias which, in the judgement of the physician, are considered as life-threatening.

Class I antiarrhythmic drugs have not been shown to improve survival in patients with ventricular arrhythmias.

4.2 Posology and method of administration

Posology

Treatment with mexiletine should be initiated and monitored by a specialist experienced in the treatment of cardiac arrhythmias.

The optimal dosage should be determined individually based on the patient's response and tolerance.

Adults

In patients in whom rapid control of ventricular arrhythmia is needed, a loading dose of 400 mg may be given.

A maintenance dose of 150 mg to 300 mg, two to three times daily is recommended.

If necessary, dose may be adjusted in 50 or 100 mg increments. A minimum of two to three days between dose adjustments is recommended.

Dosage should not exceed 1200 mg per day.

Paediatric population

The safety and efficacy of Mexiletine Hard Capsules in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Elderly

No dosage adjustment is required for older patients with normal renal function.

Renal impairment

No dosage adjustment is considered necessary in patients with mild or moderate renal impairment. There is no clinical experience in patients with severe renal impairment (creatinine clearance <30 ml/min), therefore mexiletine should not be used in these patients (see section 5.2).

Hepatic impairment

It is recommended to exercise caution in patients with mild or moderate hepatic impairment due to the potential for higher plasma exposure. In those patients, a minimum of two weeks between dose adjustments is recommended. Mexiletine should not be used in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Poor CYP2D6 metabolisers

The major elimination pathway for mexiletine is through CYP2D6. There is a potential for increased plasma levels in CYP2D6 poor metabolisers (7% of the European population). In those patients, a minimum of one week between dose adjustments is recommended. (see sections 4.4 and 5.2).

Method of administration

For oral use. Capsules should be swallowed whole with ample liquid, preferably with the patient in an upright position.

It is advisable to take Mexiletine Hard Capsules with food to minimise gastrointestinal adverse effects.

4.3 Contraindications

- Hypersensitivity to mexiletine hydrochloride or local anaesthetics of amide type
- Hypersensitivity to any of the excipients listed in Section 6.1
- Sinus node dysfunction (unless a pacemaker is present)
- Severe atrioventricular (AV) conduction disturbances (unless a pacemaker is present)
- Severe heart failure (HF); cardiogenic shock

4.4 Special warnings and precautions for use

Considering the pro-arrhythmic potential of mexiletine and the lack of evidence of improved survival for class I antiarrhythmic agents in patients without life-threatening arrhythmias, the use of mexiletine should be reserved for patients with life-threatening ventricular arrhythmia.

Congestive Heart Failure (CHF) or Hypotension

Mexiletine should be used with caution in patients with hypotension or congestive heart failure because of its potential for depressing myocardial contractility.

Conduction Abnormalities

Caution should be exercised when mexiletine is used in patients with first degree AV block or intraventricular conduction abnormalities.

If a ventricular pacemaker is operative, patients with second- or third-degree AV block may be treated with mexiletine if continuously monitored.

Blood Dyscrasias

Leukopenia and thrombocytopenia have been reported in clinical studies.

It is recommended that careful hematologic monitoring should be carried out in patients on mexiletine. Haemogram including WBC differential and platelet count should be performed prior to initiation of therapy. If significant hematologic changes are observed, the patients should be carefully evaluated, and, if warranted, mexiletine should be discontinued. Blood counts usually returned to normal within one month of discontinuation.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

DRESS refers to syndrome characterised by severe cutaneous eruptions, fever, lymphadenopathy, hepatitis, haematological abnormalities with eosinophilia and atypical lymphocytes and can involve other organs. The latency between drug initiation and onset of disease is prolonged, typically between one to eight weeks. Severe systemic manifestations are responsible for a 10% mortality rate. Incidence of DRESS has been reported between 1:100 and 1:10,000 patients treated.

Several medicinal products including mexiletine have been identified as possible causes. Mexiletine should not be administered to patients with known hypersensitivity to mexiletine or any of the excipients of this product or to any local anaesthetic.

CYP2D6 polymorphism

CYP2D6 polymorphism may affect mexiletine pharmacokinetics (see section 5.2). High mexiletine plasma levels may by observed in patients with CYP2D6 poor metabolism or in patients who take medicinal products that inhibit CYP2D6 (see section 4.5). If necessary, dose increase is recommended after a period of at least 7 days to ensure that steady-state levels are reached and mexiletine is well tolerated.

Smoking

Mexiletine pharmacokinetics are affected by cigarette smoking and the doses of mexiletine may need to be increased or decreased, if patients start or stop smoking, respectively (see section 4.5).

Patients with Liver Disease

Mexiletine should be used with caution in patients with mild or moderate hepatic dysfunction. Mexiletine should not be used in patients with severe hepatic impairment.

Liver Injury

Abnormalities of the liver function and rare instances of severe liver injury, including hepatic necrosis have been reported in association with mexiletine treatment. It is recommended that patients in whom an abnormal liver test has occurred, or who have signs or symptoms suggesting liver dysfunction, be carefully evaluated. If persistent or worsening elevation of hepatic enzymes is detected, considerations should be given to discontinuing therapy.

Urinary pH

Since renal excretion of mexiletine is greatly increased with acidification of urine, concomitant drug therapy or dietary regimens which substantially change urinary pH should be avoided while being treated with mexiletine.

Seizures

Mexiletine Capsules should be used with caution in patients with history of seizures.

Occupational Hazards

Mexiletine causes CNS effects and patients should be warned about engaging in activities requiring mental alertness, judgement and physical coordination when these effects occur.

Electrolyte Disturbances

Antiarrhythmic drugs may be ineffective in patients with electrolyte disturbances. Therefore, any electrolyte disturbances should be corrected as part of the management of ventricular arrhythmia. Electrolytic evaluation should be done prior to initiating and during therapy with mexiletine in every patient.

Mexiletine hydrochloride 100 mg Hard Capsules and Mexiletine hydrochloride 200 mg Hard Capsules contain sodium.

These medicines contain less than 1 mmol sodium (23 mg) per capsule, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Co-administration of mexiletine and antiarrhythmics inducing torsades de pointes (Class Ia: quinidine, procainamide, disopyramide, ajmaline; Class Ic: encainide, flecainide, propafenone, moricizine; Class III: amiodarone, sotalol, ibutilide, dofetilide, dronedarone, vernakalant) increases the risk of potentially lethal torsades de pointes.

Co-administration of mexiletine and other classes of antiarrhythmics (Class Ib: lidocaine, phenytoin, tocainide; Class II: propranolol, esmolol, timolol, metoprolol, atenolol, carvedilol, bisoprolol, nebivolol; Class IV: verapamil, diltiazem) increase the risk of adverse cardiac reactions.

Pharmacokinetic interactions

Effect of other medicinal products on mexiletine

Medicinal products that delay gastric-emptying, such as opioids, antacids and atropine may delay the absorption of mexiletine. Similarly, drugs that accelerate gastric-emptying, such as metoclopramide may reduce the time to peak mexiletine concentrations and increase peak concentrations.

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 concentrations of mexiletine.

Co-administration of mexiletine with CYP1A2 inhibitors such as ciprofloxacin, fluvoxamine and propafenone or CYP2D6 inhibitor such as propafenone and quinidine significantly increases mexiletine exposure resulting in increased risk of adverse reactions.

Co-administration of mexiletine with CYP1A2 inducers such as omeprazole or CYP2D6 inducers such as phenytoin and rifampicin may increase the clearance and elimination rate of mexiletine due to an increased hepatic metabolism, resulting in decreased plasmatic concentrations and half-life of mexiletine.

Cigarette smoking may increase the total clearance of mexiletine. Mexiletine dose may need to be adjusted in smokers.

Effect of mexiletine on other medicinal products

Co-administration of mexiletine with medicinal products metabolised by CYP1A2, such as theophylline, caffeine, lidocaine or tizanidine, may be associated with elevations in plasma concentrations of the concomitant medicine that could increase or prolong the therapeutic efficacy and/or the adverse reactions, especially if mexiletine is co-administered with CYP1A2 substrates with narrow therapeutic window, such as theophylline and tizanidine. The CYP1A2 substrate blood levels should be monitored.

Mexiletine may reduce the clearance of caffeine. Increased concentrations of caffeine occurring with the co-administration of mexiletine may be of concern in patients with cardiac arrhythmias.

Mexiletine may interact with drugs transported by OCT2 such as metformin and dofetilide and the OCT2 substrate blood levels should be monitored. A dose adjustment of the OCT2 substrate may be necessary.

Concomitant administration of mexiletine with warfarin may increase the risk of bleeding.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of mexiletine in pregnant women. Limited clinical data of the use of mexiletine in pregnant women shows that mexiletine crosses the placenta and reaches the foetus. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3). As a precautionary measure, it is preferable to avoid the use of mexiletine during pregnancy.

Breast-feeding

Mexiletine is excreted in human milk. There is insufficient information on the effects of mexiletine in newborns/infants. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from mexiletine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effects of mexiletine on fertility in humans have not been studied. Animal studies with mexiletine do not indicate harmful effects with respect to fertility (see Section 5.3).

4.7 Effects on ability to drive and use machines

The ability to drive or operate machinery may be impaired in patients under mexiletine treatment.

Simultaneous intake of alcohol may further affect the ability to drive and use machines.

4.8 Undesirable effects

Adverse effects have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000; <1/100); rare (≥1/10,000; <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

System Organ Class	**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 established from the available data)**
Blood and lymphatic system disorders				neutropenia, agranulocytosis		leukopenia, thrombocytopenia
Immune system disorders					drug reaction with eosinophilia and systemic symptoms (DRESS)	lupus like syndrome, dermatitis exfoliative, Stevens-Johnson syndrome

System Organ Class	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 established from the available data)
Psychiatric disorders	insomnia	somnolence				hallucinations, confusional state
Nervous system disorders	dizziness, tremor,	headache, paraesthesia, vision blurred, numbness	seizure, speech disorders, amnesia, lost consciousness			diplopia, dysgeusia
Ear and labyrinth disorders		vertigo, tinnitus				
Cardiac disorders		tachycardia, palpitations, angina pain, atrial fibrillation,	bradycardia	heart failure		atrioventricular block
Vascular disorders		flushing, hypotension				circulatory collapse, hot flush
Respiratory, thoracic and mediastinal disorders			hiccups			pulmonary fibrosis
Gastrointestinal disorders	abdominal pain, dyspepsia	nausea, constipation, dry mouth				diarrhoea, vomiting, oesophageal ulcers and perforation
Hepatobiliary disorders				hepatic function abnormal	drug-induced liver injury, liver disorder, hepatitis	
Skin and subcutaneous tissue disorders		acne, rash	dry skin, alopecia			
Musculoskeletal and connective tissue disorders		pain in the extremities	arthralgia			

System Organ Class	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 established from the available data)
General disorders and administration site conditions		fatigue, asthenia, chest discomfort, malaise, ataxia				
Investigations			abnormal liver function tests			
Reproductive system and breast disorders			impotence			

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms

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

The clinical features include: nausea, hypotension, bradycardia, paraesthesia, left bundle branch block, asystole convulsions and death.

Management and treatment

Treatment should be supportive and may include gastric lavage and atropine for cardiovascular complications. Intravenous administration of 0.5-1.0 mg atropine or 0.5-1.0 mg ipratropium bromide is recommended.

Benzodiazepines have a protective effect against mexiletine induced convulsions.

Acidification of the urine enhances mexiletine elimination.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, antiarrhythmics, Class Ib

ATC code: C01BB02

Mechanism of action

Mexiletine is a local anaesthetic, antiarrhythmic agent, structurally similar to lidocaine. Mexiletine is effective in the suppression of induced ventricular arrhythmias. Mexiletine, like lidocaine inhibits the inward sodium current, thus reducing the rate of rise of the action potential, Phase 0. Mexiletine decreases the Effective Refractory Period (ERP) in Purkinje fibers. The decrease in ERP is of lesser magnitude than the decrease in Action Potential Duration (APD), with a resulting increase in the ERP/APD ratio.

Pharmacodynamic effects

Mexiletine does not usually alter conduction velocity, although it may slow conduction in patients with pre-existing conduction abnormalities. In those with pre-existing sick sinus syndrome, mexiletine produces a more pronounced depression of the sinus rate and/or prolongation of sinus node recovery time. It does not significantly affect resting membrane potential or sinus node automaticity, left ventricular function, systolic arterial blood pressure, Atrioventricular (AV) conduction velocity, QRS or QT intervals.

Haemodynamic studies with oral mexiletine conducted in patients with normal or abnormal myocardial function have demonstrated that the drug usually has only minor effects on cardiac output, pulmonary capillary wedge pressure, left ventricular end–diastolic pressure, pulmonary diastolic pressure, blood pressure or heart rate.

Clinical efficacy and safety

In patients with normal conduction systems, Mexiletine has a minimal effect on cardiac impulse generation and propagation. In clinical trials, no development of second-degree or third-degree AV block was observed. Mexiletine did not prolong ventricular depolarization (QRS duration) or repolarization (QT intervals) as measured by electrocardiography. Theoretically, therefore, Mexiletine may be useful in the treatment of ventricular arrhythmias associated with a prolonged QT interval.

In patients with pre-existing conduction defects, depression of the sinus rate, prolongation of sinus node recovery time, decreased conduction velocity and increased effective refractory period of the intraventricular conduction system have occasionally been observed.

The antiarrhythmic effect of Mexiletine has been established in controlled comparative trials against placebo, quinidine, procainamide and disopyramide. Mexiletine, at doses of 200-400 mg q8h, produced a significant reduction of ventricular premature beats, paired beats, and episodes of non-sustained ventricular tachycardia compared to placebo and was similar in effectiveness to the active agents. Among all patients entered into the studies, about 30 % in each treatment group had a 70 % or greater reduction in PVC count and about 40 % failed to complete the 3 month studies because of adverse effects. Follow-up of patients from the controlled trials has demonstrated continued effectiveness of Mexiletine in long-term use.

Paediatric population

The safety and efficacy of Mexiletine Hard Capsules in children and adolescents aged 0 to 18 years have not yet been established.

5.2 Pharmacokinetic properties

Absorption

Mexiletine is readily absorbed from the gastrointestinal tract. Peak plasma concentrations are attained within 2 to 4 hours after oral administration. The systemic bioavailability of mexiletine is about 90 %.

The therapeutic range is approximately 0.5 to 2.0 μg/ml.

The pharmacokinetic parameters of mexiletine are not affected by food intake, however it is advisable to take mexiletine after food in order to reduce the incidence of gastrointestinal adverse effects.

Distribution

The apparent volume of distribution is large (5 to 10 L/kg) reflecting the extensive uptake of the drug by tissues.

Protein binding has been estimated to be about 55 to 70 %.

Mexiletine crosses the placental barrier and diffuses into breast milk.

Biotransformation

Mexiletine is mainly (90%) metabolized in the liver by CYP2D6 enzymes and is also a substrate of CYP1A2. Its metabolic pathways include aromatic and aliphatic hydroxylation, dealkylation, deamination and N-oxidation. Mexiletine metabolites are submitted to further conjugation with glucuronic acid (phase II metabolism) with major metabolites being p-hydroxymexiletine, hydroxy-methylmexiletine and N-hydroxymexiletine.

Mexiletine pharmacokinetics are characterised by significantly lower total and renal clearance resulting in prolonged elimination half-life, higher exposure and lower volume of distribution in poor CYP2D6 metabolisers compared to extensive metabolisers.

Approximately 10 % is excreted unchanged by the kidney.

Elimination

The elimination half-life is 5 - 15 hours. Excretion of mexiletine essentially occurs through the kidney (90 % of the dose, including 10 % as unchanged mexiletine).

Renal clearance varies with urine pH, but this is unlikely to have clinical significance.

Linearity/non-linearity

A linear relationship between mexiletine dose and plasma concentration has been observed in the dose range of 50 to 600 mg.

Special populations

Hepatic impairment prolongs the elimination half-life of mexiletine. In eight patients with moderate to severe liver disease, the mean half-life was approximately 25 hours.

Consistent with the limited renal elimination of mexiletine, little change in the half-life has been detected in patients with reduced renal function. In eight patients with creatinine clearance less than 10 ml/min, the mean plasma elimination half-life was 15.7 hours; in seven patients with creatinine clearance between 11-40 ml/min, the mean half-life was 13.4 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development. The main observed effects in rats and/or dogs were vomiting, diarrhoea, tremor, ataxia, convulsions and tachycardia, however these effects are of unclear clinical relevance.

Previous studies in rats on carcinogenic potential had negative results but this result is of unclear clinical relevance as there are no data from studies performed in accordance with current standards.

The negative genotoxicity potential does not indicate an increased carcinogenic risk of treatment with mexiletine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Maize starch

Silica, colloidal anhydrous

Magnesium stearate (E572)

Capsule shell:

Indigotine – FD&C Blue 2 (E132) (including traces of sodium)

Titanium dioxide (E171)

Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

27 months.

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

Mexiletine Hard Capsules are packed in PVC/PVDC/aluminium blisters. Each blister contains 10 or 14 capsules.

Pack sizes: 30, 50, 56, 84, 100, 200 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Clinigen Healthcare Ltd.

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8 MARKETING AUTHORISATION NUMBER(S)

PL 31644/0029

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/06/2021

10 DATE OF REVISION OF THE TEXT

30/09/2024