New Medicine Assessment

MEXILETINE CAPSULES (ORAL)

Recommendation: RED for the following indications:

The treatment of documented ventricular arrhythmias which, in the judgement of the physician, are considered as life-threatening.

Summary of supporting evidence:

- Despite some limitations in the available evidence, it is accepted that there is sufficient evidence to support the efficacy of mexiletine in preventing premature ventricular contractions (PVCs) and supressing ventricular arrythmias in different conditions.
- The impact on long term clinical outcomes is uncertain, and the SPC includes a warning that treatment with mexiletine may not prolong life.
- In large clinical trials such as CAST and CASH, sodium channel-blocking drugs increased mortality among patients with previous myocardial infarction.
- There is little prospect of repeating the original trials of anti-arrhythmic drugs, so the therapeutic implications of the original trials must be extrapolated to the modern context.
- As a general rule, anti-arrhythmic agents may be effective as adjunctive therapy in the management of arrhythmia prone patients under specific circumstances.
- There is a paucity of data to guide combination therapy with antiarrhythmic drugs, and such combinations should be reserved for patients in whom other anti-arrhythmic treatments (including single-agent anti-arrhythmic drug therapy with different agents, amiodarone therapy and catheter ablation) have been tried without satisfactory suppression of arrhythmia episodes.
- 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.
- Consideration should be given to the risk of DRESS syndrome, blood dyscrasias and liver injury; appropriate monitoring arrangements should be in place.
- Prescribers should be aware of and act on drug and non-drug interactions with mexiletine, for example with caffeine and in patients that smoke.
- The cost of mexiletine in the community could be prohibitive. All strengths of capsule are of high cost, but patient numbers are likely to be low. The tariff price of the 200mg capsule (brand licensed for myotonia) could make treatment costs unfeasible if used.

Details of Review

Name of medicine (generic & brand name)**:**

Mexiletine hydrochloride

Strength(s) and form(s):[1]

Mexiletine hydrochloride 50mg Hard Capsules (equivalent to 41.55mg of mexiletine)

Mexiletine hydrochloride 100mg Hard Capsules (equivalent to 83.10mg of mexiletine)

Mexiletine hydrochloride 200mg Hard Capsules (equivalent to 166.20mg of mexiletine)

Mexiletine (Namuscla) 167mg Hard Capsules (equivalent to 200mg mexiletine hydrochloride)

Dose and administration:

Ventricular arrhythmias which, in the judgement of the physician, are considered as life-threatening1

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.

Myotonia[2]

The recommended starting dose of mexiletine is 167 mg daily (1 capsule per day). After at least 1 week of treatment, based on the clinical response, the daily dose can be increased to 333 mg daily (2 capsules per day). After at least 1 further week of treatment, based on clinical response, dose can be further increased to 500 mg daily (3 capsules per day).

Maintenance treatment is between 167 mg – 500 mg daily (1 to 3 capsules per day), according to the intensity of symptoms and the clinical response, taken regularly throughout the day.

The dose should not exceed 500 mg/day. Regular reassessment should be implemented, not to continue long-term treatment in a patient not responding or not experiencing benefit of the treatment.

Before starting mexiletine treatment, detailed and careful cardiac evaluation should be carried out; throughout treatment with mexiletine, cardiac monitoring needs to be continued and adapted as a function of the heart condition of the patient

BNF therapeutic class / mode of action:

Arrhythmias > Anti-arrhythmic drugs > Ventricular arrhythmias >

Mexiletine is a sodium channel blocker with anti-arrhythmic and muscle relaxant properties.

Licensed indication(s):

1. 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.

2. Namuscla is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

Proposed use (if different from, or in addition to, licensed indication above):

Documented ventricular arrhythmias which, in the judgement of the physician, are considered as life-threatening.

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

Dosage should not exceed 1200 mg per day.

Mexiletine 50mg capsules = £185 (pack size 84)

Mexiletine 100mg capsules = £375 (pack size 84)

Mexiletine 200mg capsules (Namuscla)* = £5000 (pack size 100)

150mg bd = **£373** per month

300mg tds = **£1125** per month (3x100mg tds), or **£4575** per month (1x200mg + 1x100mg tds)

Max 1200mg per day = **£1500** per month (4x100mg tds), or **£8,400** (2x200mg tds) per month.

*Namuscla brand 200mg capsules are licensed for myotonia, not ventricular arrhythmias. A range of other manufacturers produce mexiletine 200mg capsules at a substantially lower price, however the tariff price for 100 x 200mg capsules is currently £5000.

Prices as per drug tariff July 2022

Current standard of care/comparator therapies:

Ventricular arrhythmias:[3]

- **Amiodarone** hydrochloride is used in the treatment of arrhythmias, particularly when other drugs are ineffective or contraindicated. It should be initiated only under hospital or specialist supervision. Amiodarone hydrochloride may be given by intravenous infusion as well as by mouth and has the advantage of causing little or no myocardial depression.
- **Sotalol** hydrochloride has a role in the management of ventricular arrhythmias. Beta-blockers act as anti-arrhythmic drugs principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart.
- **Disopyramide** can be given by intravenous injection to control arrhythmias after myocardial infarction (including those not responding to lidocaine hydrochloride), but it impairs cardiac contractility. Oral administration of disopyramide is useful, but it has an antimuscarinic effect which limits its use in patients susceptible to angle-closure glaucoma or with prostatic hyperplasia.
- **Flecainide** acetate belongs to the same general class as lidocaine hydrochloride and may be of value for serious symptomatic ventricular arrhythmias. However, it can precipitate serious arrhythmias in a small minority of patients (including those with

otherwise normal hearts).

- **Propafenone** hydrochloride is used for the prophylaxis and treatment of ventricular arrhythmias and also for some supraventricular arrhythmias. It has complex mechanisms of action, including weak beta-blocking activity (therefore caution is needed in obstructive airways disease—contra-indicated if severe).
- **Lidocaine** hydrochloride can be used intravenously for the treatment of ventricular tachycardia in haemodynamically stable patients, and ventricular fibrillation and pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation, however it is no longer the anti-arrhythmic drug of first choice.
- **Procainamide** is available from 'special-order' manufacturers or specialist importing companies.

Relevant NICE guidance:

NG196 Atrial fibrillation: diagnosis and management (April 2021)

TA314 Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (June 2014)

TA748 Mexiletine for treating the symptoms of myotonia in non-dystrophic myotonic disorders (Dec 2021)

Background and context

Arrhythmia is a condition where the heart contracts irregularly, or at a faster or slower pace than normal. It is caused by an abnormality in the myocardial tissue, or in the electrical conduction system of the heart. Arrhythmias that arise from ventricles (ventricular arrhythmias) can occur unexpectedly and can cause sudden death when insufficient blood is pumped out by the heart to sustain life. Ventricular arrhythmias include ventricular tachycardia and ventricular fibrillation. In ventricular tachycardia, the ventricles beat faster than normal (at between 120 and 200 beats per minute). In ventricular fibrillation, electrical impulses rapidly start firing from multiple sites in the ventricles, resulting in an uncoordinated, irregular rhythm.

Ventricular arrhythmias most commonly occur in people with underlying heart disease. Approximately 75–80% of the 70,000 sudden cardiac deaths in England and Wales in 2010 could be attributed to ventricular arrhythmias. The average chance of survival of adults after an out-of-hospital episode of ventricular arrhythmia has been reported to be as low as 7%. However, with appropriate treatment, recent studies have reported 5-year survival of 69-100% in people who had survived a cardiac arrest.

Many patients presenting with arrhythmias, with or without symptoms, are treated with antiarrhythmic drug therapy. However, antiarrhythmic drugs may not be optimally effective and need careful and frequent adjustment. This can be confusing for patients and may lead to missed doses, taking the wrong dose or overdose. Many antiarrhythmic drugs result in tiredness, inability to perform day-to-day activities and dependence on carers, and consequently increase the risk of depression. Antiarrhythmic drugs also have many side effects on a range of organs including the thyroid, liver and lungs.

Chronic prophylactic antiarrhythmic drug therapy aims to suppress the development of arrhythmias, but does not stop an arrhythmia once it has started. People who survive a first episode of life-threatening ventricular arrhythmia are at high risk of further episodes. For preventing further life-threatening events in survivors of previous serious ventricular arrhythmias, people are usually treated with implantable cardioverter defibrillators (ICDs). Preventing sudden cardiac death in someone who has never had a cardiac arrest or ventricular arrhythmia is challenging because it requires identifying a person with substantial level of risk. Many risk factors for sudden cardiac death have been reported such as age, hereditary factors, having a high risk for coronary artery disease, inflammatory markers, hypertension, left ventricular hypertrophy, conduction abnormalities (for example, left bundle branch block), obesity, diabetes and lifestyle factors. There is currently no optimal strategy for risk stratification.[4]

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 fibres. The decrease in ERP is of a lesser magnitude than the decrease in Action Potential Duration (APD), with a resulting increase in the ERP/APD ratio.[5]

Summary of evidence

Summary of efficacy data in proposed use:

MHRA Public Assessment Report (PAR) 2021[5]

Based on the review of the data on quality, safety and efficacy, the MHRA considered the applications for Mexiletine hydrochloride 50, 100 and 200mg Hard Capsules could be approved. National marketing authorisations were granted in the UK on 17th June 2021. The PD, PK and toxicological properties of mexiletine hydrochloride are well known, therefore the applicant has not

provided additional studies and further studies are not required.

The efficacy review was based on a large number of published studies which generally support the antiarrhythmic properties of mexiletine in different settings. Despite some limitations in the available evidence, it is accepted that there is sufficient evidence to support the efficacy of mexiletine in preventing premature ventricular contractions (PVCs) and supressing ventricular arrythmias in different conditions. Yet the impact on long term clinical outcomes is uncertain, and the SPC includes a warning that treatment with mexiletine may not prolong life. This is related to the findings of the CAST trial published in 1989, which showed that the suppression of PVCs in post MI patients resulted in excessive mortality compared to placebo; although in that study class 1C antiarrhythmics were tested, the warning, extrapolating the findings to the whole class I members, was also included in the originator Mexitil SPC.

Overall, the data provided supported the efficacy and safety of mexiletine in the treatment of ventricular arrhythmias and is an effective antiarrhythmic agent which may be useful in the management of certain patients.

SIGN 152 Cardiac arrhythmias in coronary heart disease 2018[6]

Routine use of antiarrhythmic drugs is not recommended following ACS.

Mexiletine is not mentioned directly in the guideline.

AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death 2017[7]

With the exception of beta blockers, there is no evidence from RCTs that antiarrhythmic medications for VA improve survival when given for the primary or secondary prevention of SCD. However, the use of these medications is essential in some patients to control arrhythmias and improve symptoms.

Except in specific circumstances, sodium channel blockers (Vaughn-Williams class I agents) have a limited role in the prevention of VT/SCD; this is based on a lack of survival benefit and increased mortality observed during chronic therapy in patients with ischemic heart disease. In large clinical trials, sodium channel blockers increased mortality among patients convalescing from MI, but similar trends were also seen with earlier trials of mexiletine and disopyramide.

Specific circumstances where sodium channel blockers have been used to treat VT/SCA include: intravenous lidocaine for patients with refractory VT/cardiac arrest (especially witnessed); oral mexiletine for congenital long QT syndrome; quinidine for patients with Brugada syndrome; and flecainide for patients with catecholaminergic polymorphic ventricular tachycardia. These medications could also be used in ICD patients with drug- and ablation-refractory VT.

ESC Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death Guidelines 2015[8]

The treatment of heart disease has changed considerably since the seminal trials of anti-arrhythmic drugs and the ICD were undertaken. As there is little prospect of repeating such trials, the therapeutic implications of the original trials must be extrapolated to the modern context.

With the exception of beta-blockers, currently available antiarrhythmic drugs have not been shown in randomized clinical trials (RCTs) to be effective in the primary management of patients with life-threatening VAs or in the prevention of SCD. Occasional studies with amiodarone have shown positive results, but this is not a consistent finding. As a general rule, anti-arrhythmic agents may be effective as adjunctive therapy in the management of arrhythmia prone patients under specific circumstances. Because of potential adverse effects of anti-arrhythmic drugs, they must be used with caution.

There is a paucity of data to guide combination therapy with antiarrhythmic drugs, and such combinations should be reserved for patients in whom other anti-arrhythmic treatments (including single-agent anti-arrhythmic drug therapy with different agents, amiodarone therapy and catheter ablation) have been tried without satisfactory suppression of arrhythmia episodes. In patients with

frequent VT, combinations of sodium channel blockers and potassium channel blockers (e.g. mexiletine and sotalol, or amiodarone and flecainide/propafenone) have been used, usually in patients with frequent VT recurrences who have a defibrillator. Beta-blocker therapy in combination with amiodarone reduces the number of ICD shocks; however, side effects may result in drug discontinuation in a significant number of patients. Ranolazine has been combined with other anti-arrhythmic agents to suppress VT in otherwise drug-refractory cases. Careful monitoring of the ECG and cardiac function is needed to detect deterioration of LV function and/or signs of pro-arrhythmia in such patients.

EHRA/HRS/APHRS expert consensus on ventricular arrhythmias 2014[9]

The spectrum of VAs ranges from those that are benign and asymptomatic to those that produce severe symptoms including sudden cardiac death (SCD). In addition, many patients exhibit multiple forms of VAs over time. Most medical interventions to prevent sudden death and to treat VAs were developed in an era when patient cohorts were small and the accepted standards to demonstrate effectiveness were lower than today. Many interventions to terminate or suppress VAs have since been used in many patients, and over time different treatment 'patterns' have developed in different regions of the world.

In patients who suffer from symptomatic non-sustained VAs on an adequately dosed beta-blocker or a non-dihydropyridine calcium channel antagonist, treatment with an antiarrhythmic drug (AAD; amiodarone, flecainide, mexiletine, propafenone, sotalol) may be considered to improve symptoms associated with arrhythmia episodes.

For patients with structural heart disease (SHD) and recurrent Sustained monomorphic ventricular tachycardia (SMVT), specific treatment of VAs with AADs (amiodarone, mexiletine, or sotalol), catheter ablation, and/or anti-tachycardia pacing (ATP) from an ICD should be considered in addition to an ICD.

Cochrane systematic review on prophylactic lidocaine for myocardial infarction 2015[10]

Overall, trials had high risks of bias and were underpowered.

Non-pooled trials examining lidocaine versus tocainide or mexiletine did not differ significantly in terms of all-cause mortality. Similarly, lidocaine did not differ significantly from tocainide and mexiletine in terms of cardiac mortality.

Lidocaine compared with placebo or no intervention, disopyramide, mexiletine and propafenone did not significantly reduce the proportions of participants developing ventricular fibrillation.

VANISH trial 2016[11]

A multi-centre, randomised, controlled trial involving patients with ischemic cardiomyopathy and an ICD who had ventricular tachycardia despite the use of antiarrhythmic drugs.

Patients were eligible for inclusion if they had had a myocardial infarction, had undergone placement of an ICD, and had had an episode of ventricular tachycardia during treatment with amiodarone or another class I or class III AAD within the previous 6 months.

Patients were randomly assigned to receive either catheter ablation (ablation group) with continuation of baseline antiarrhythmic medications or escalated antiarrhythmic drug therapy (escalated-therapy group). In the escalated therapy group, amiodarone was initiated if another agent had been used previously. The dose of amiodarone was increased if it had been less than 300 mg per day or mexiletine was added (200mg three times daily) if the dose was already at least 300 mg per day. The primary outcome was a composite of death, three or more documented episodes of ventricular tachycardia within 24 hours (ventricular tachycardia storm), or appropriate ICD shock.

Of the 259 patients who were enrolled, 132 were assigned to the ablation group and 127 to the escalated-therapy group. During a mean (±SD) of 27.9±17.1 months of follow-up, the primary outcome occurred in 59.1% of patients in the ablation group and 68.5% of those in the escalated-

therapy group (hazard ratio in the ablation group, 0.72; 95% confidence interval, 0.53 to 0.98; P=0.04). The rate of the primary outcome was significantly lower in the ablation group than in the escalated-therapy group. There was no significant between-group difference in mortality. There were two cardiac perforations and three cases of major bleeding in the ablation group and two deaths from pulmonary toxic effects and one from hepatic dysfunction in the escalated-therapy group.

In patients with ischemic cardiomyopathy and an ICD who had ventricular tachycardia despite antiarrhythmic drug therapy, there was a significantly lower rate of the composite primary outcome of death, ventricular tachycardia storm, or appropriate ICD shock among patients undergoing catheter ablation than among those receiving an escalation in antiarrhythmic drug therapy.

Summary of safety data:

MHRA Public Assessment Report 2021[5]

In general, the safety profile of mexiletine is well established.

Extensive clinical experience with mexiletine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is therefore considered to be positive.

Haemodynamic studies suggest that oral administration of mexiletine, depending on dose, may have a small negative effect on cardiac output (may increase systemic vascular resistance, but no significant negative inotropic effect). BP and HR are not normally affected.

Mexiletine should be used with caution in patients with mild or moderate liver dysfunction.

Mexiletine should not be used in patients with severe liver disease or severe kidney disease.

There is potential for increased plasma levels in CYP2D6 poor metabolisers (7% of the European population).

The most common adverse effects with mexiletine are abdominal pain, dyspepsia, insomnia, dizziness and tremor.

EMA EPAR Namuscla (mexiletine HCl) 2019[12]

Licensed for myotonia.

The most common side effects with Namuscla (which may affect more than 1 in 10 people) are abdominal pain and insomnia. The most serious side effects reported (which may affect up to 1 in 10,000 people) are arrhythmias and a severe reaction affecting skin, blood and internal organs, known as drug reaction with eosinophilia and systemic symptoms (DRESS).

ESC Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death Guidelines 2015[8]

Anti-arrhythmic drugs have direct effects on cardiac ion channels. Flecainide, propafenone and quinidine have sodium channel blocking effects. In large clinical trials such as CAST and CASH, sodium channel-blocking drugs increased mortality among patients with previous myocardial infarction. Similar trends were seen in earlier trials of mexiletine and disopyramide. In patients treated for sustained VT, these agents may provoke more frequent, and often more difficult to cardiovert, episodes of sustained VT.

Cochrane systematic review on prophylactic lidocaine for myocardial infarction 2015[10]

Lidocaine compared with placebo or no intervention significantly increased risks of asystole, drowsiness and dizziness. No significant differences were noted between lidocaine and disopyramide, tocainide, mexiletine, propafenone, amiodarone, dimethylammonium and aprindine in terms of adverse events - cardiovascular or neurological. However, safety data were poorly reported overall, and adverse events may be underestimated. No trials reported data on overall

survival at 30 days after myocardial infarction.

Summary of Product Characteristics1

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

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

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.

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.

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.

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.

Contraindications

• Hypersensitivity to mexiletine hydrochloride or local anaesthetics of amide type

• Hypersensitivity to any of the excipients

• Sinus node dysfunction (unless a pacemaker is present)

• Severe atrioventricular (AV) conduction disturbances (unless a pacemaker is present)

• Severe heart failure (HF); reduced left ventricular ejection fraction (LVEF); cardiogenic shock

• Inherited Long QT syndrome (LQTS) (other than LQTS3)

• Concomitant treatment with medicines associated with QT-interval prolongation

Interactions

Mexiletine has numerous drug interactions and prescribers should always refer to the SPC before commencing a patient on mexiletine.

Adverse effects

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
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			
General disorders and administration site conditions		fatigue, asthenia, chest discomfort, malaise, ataxia				
Investigations			abnormal liver function tests			
Reproductive system and breast disorders			impotence			

Strengths and limitations of the evidence:

- Despite some limitations in the available evidence, it is accepted that there is sufficient evidence to support the efficacy of mexiletine in preventing premature ventricular contractions (PVCs) and supressing ventricular arrythmias in different conditions.
- The impact on long term clinical outcomes is uncertain, and the SPC includes a warning that treatment with mexiletine may not prolong life.
- Extensive clinical experience with mexiletine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is therefore considered to be positive.
- The treatment of heart disease has changed considerably since the seminal trials of anti-arrhythmic drugs and the ICD were undertaken. As there is little prospect of repeating such trials, the therapeutic implications of the original trials must be extrapolated to the modern context.

- Most medical interventions to prevent sudden death and to treat VAs were developed in an era when patient cohorts were small and the accepted standards to demonstrate effectiveness were lower than today. Many interventions to terminate or suppress VAs have since been used in many patients, and over time different treatment 'patterns' have developed in different regions of the world.
- In large clinical trials such as CAST and CASH, sodium channel-blocking drugs increased mortality among patients with previous myocardial infarction.
- In patients with ischemic cardiomyopathy and an ICD who had ventricular tachycardia despite antiarrhythmic drug therapy, there was a significantly lower rate of the composite primary outcome of death, ventricular tachycardia storm, or appropriate ICD shock among patients undergoing catheter ablation than among those receiving an escalation in antiarrhythmic drug therapy.
- There is a paucity of data to guide combination therapy with antiarrhythmic drugs, and such combinations should be reserved for patients in whom other anti-arrhythmic treatments (including single-agent anti-arrhythmic drug therapy with different agents, amiodarone therapy and catheter ablation) have been tried without satisfactory suppression of arrhythmia episodes.
- As a general rule, anti-arrhythmic agents may be effective as adjunctive therapy in the management of arrhythmia prone patients under specific circumstances.
- 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.

Summary of evidence on cost effectiveness:

None available.

Prescribing and risk management issues:

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.

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.

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

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.

Commissioning considerations:

Innovation, need and equity implications of the intervention:
None identified.
Financial implications of the intervention:

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

Dosage should not exceed 1200 mg per day.

Mexiletine 50mg capsules = £185 (pack size 84)

Mexiletine 100mg capsules = £375 (pack size 84)

Mexiletine 200mg capsules (Namuscla)* = £5000 (pack size 100)

150mg bd = **£373** per month

300mg tds = **£1125** per month (3x100mg tds), or **£4575** per month (1x200mg + 1x100mg tds)

Max 1200mg per day = **£1500** per month (4x100mg tds), or **£8400** (2x200mg tds) per month.

Estimate approximately 40 patients across LSCMMG currently prescribed mexiletine.

Numbers of patients prescribed mexiletine unlikely to be affected by RAG status.

Approximate annual cost per patient **£1,119 - £109,200**

Approximate annual cost **£44,760 - £4,368,000**

*Namuscla brand 200mg capsules are licensed for myotonia, not ventricular arrhythmias. A range of other manufacturers produce mexiletine 200mg capsules at a substantially lower price, however the tariff price for 100 x 200mg capsules is currently £5000.

Prices as per drug tariff July 2022

Service Impact Issues Identified:

Mexiletine availability in primary care may improve accessibility for patients.

Equality and Inclusion Issues Identified:

None identified

Cross Border Issues Identified:

The **Pan Mersey APC** has mexiletine listed with a Red RAG rating in their formulary (Chapter 2, cardiovascular system).

The **Greater Manchester Medicines Management Group** (GMMMG) has no entry for mexiletine on its website.

Legal Issues Identified:

None identified

Media/ Public Interest:

None identified

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

References

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