

**Module 2.5: Clinical Overview
of
Mexiletine hydrochloride
100 mg and 200 mg hard capsules**

Module 2.5 Clinical overview

The clinical overview is intended to provide a critical analysis of the clinical data of Mexiletine hydrochloride 100 mg and 200 mg hard capsules in the application dossier. The overview of clinical testing strategy is based on the information obtained from published literatures.

The Clinical Overview contains following information:

- 2.5.1 Product Development Rationale
- 2.5.2 Overview of Biopharmaceutics
- 2.5.3 Overview of Clinical Pharmacology
- 2.5.4 Overview of Efficacy
- 2.5.5 Overview of Safety
- 2.5.6 Benefits and Risks Conclusions
- 2.5.7 List of Literature References

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List of Abbreviations

AIVR	Accelerated Idioventricular Rhythm
AMI	Acute Myocardial Infarction
ANF	Antinuclear Factor
APD	Action Potential Duration
AUC	Area Under The Curve
AV	Atrioventricular
BARDI	Bayesian Adverse Reactions Diagnostic Instrument
CHF	Congestive Heart Failure
Cl/F	Clearance Over The Bioavailability
Cl _{tot}	Total Body Clearance
C _{max}	Peak Plasma Concentration
CNS	Central Nervous System
CYP	Cytochrome P
DCM	Dilated Cardiomyopathy
DIHS	Drug-Induced Hypersensitivity Syndrome
DNA	Deoxyribonucleic Acid
DRESS	Drug Reaction With Eosinophilia And Systemic Symptoms
ECG	Echocardiography
EF	Ejection Fractions
EM	Extensive Metabolizer
ERP	Effective Refractory Period
hERG	Human Ether-À-Go-Go-Related Gene
HHV	Human Herpesvirus
HMM	Hydroxymethylmexiletine
IACT	Interatrial Conduction Time
ICDs	Implantable Cardioverter-Defibrillators
ICT	Isovolumic Contraction Time
Ina	Sodium Influx
LQTS	Long QT Syndrome
LV	Left Ventricular
LVEF	Left Ventricular Dysfunction
MAA	Marketing Authorization Application
MEX, Ko 1173, MXL, MX	Mexiletine
MEX-Q	Mexiletine And Quinidine Combination

MVRC	Muscle Velocity Recovery Cycles
NYHA	New York Heart Association
OCT2	Organic Cation Transporter 2
PCR	Polymerase Chain Reaction
PER	Peak Ejection Rate
PK-PD	Pharmacokinetics-Pharmacodynamics
PM	Poor Metabolizer
p-OHMEX, POH, PHM	p-Hydroxymexiletine
PVCs	Premature Ventricular Complexes
Q	Quinidine
RV	Right Ventricular
RVEF	Right Ventricular Ejection Fraction
SmPC	Summary Of Product Characteristics
$t_{1/2}$	Half-Life
t_{max}	Time Taken For Peak Plasma Concentration
V_d	Volume Of Distribution
$V_{d_{tot}}$	Total Volume Of Distribution
VEDs	Ventricular Ectopic Depolarizations
VF	Ventricular Fibrillation
VPBs	Ventricular Premature Beats
VPC	Ventricular Premature Complex
VPCs	Ventricular Premature Contractions
V_{ss}	Volume Of Distribution At Steady State
VT	Ventricular Tachycardia
WMS	Wall Motion Score

2.5.1 Product Development Rationale

The management of ventricular arrhythmias has dramatically changed over the last decades. Significant achievements in defibrillator and catheter ablation therapy as well as the concern about serious drug-related side effects have resulted in a decline in antiarrhythmic drug therapy with only few evolving drug developments in the field of arrhythmias. This is reflected by a steady increase in defibrillator implantations and catheter ablations of supra- and ventricular tachyarrhythmias in patients with or without structural heart disease. In spite of these advances, there is still a relevant number of patients with ventricular arrhythmias who require (additional) antiarrhythmic drug therapy and may benefit from drugs known for decades. Mexiletine was developed by Boehringer Ingelheim (Mexitil®) in the late 1960s and showed its first positive clinical results in 1973 in a study by [REDACTED] who tested it in suppressing ventricular arrhythmias mainly occurring after myocardial infarction or induced by digitalis toxicity. Afterwards, mexiletine was increasingly used as an antiarrhythmic drug and continued to prove its effectiveness with an acceptable safety profile among various groups of patients for a long period of time. According to Vaughan-Williams's classification, mexiletine belongs to class IB of antiarrhythmic drugs by blocking sodium channels in cardiomyocytes. Owing to its molecular similarities to lidocaine, mexiletine is also referred to as "oral lidocaine" [REDACTED]

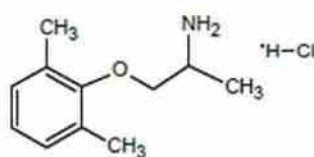
Mexiletine capsules was first introduced into the European market more than 10 years ago. This Marketing Authorization Application (MAA) is submitted by Waymade Plc UK as a "Well Established use application (Article 10a of Directive 2001/83/EC)". The scientific literatures demonstrated that the active substance in Mexiletine hydrochloride 100 mg and 200 mg hard capsules have well established medicinal use with acceptable efficacy and safety.

As this is a bibliographic application, no new clinical studies for this submission have been conducted to support this application. Therefore, this Overview summarizes the relevant pharmacodynamics, pharmacokinetic and clinical data on Mexiletine hydrochloride hard capsules found in published literatures and approved packages of already registered brands of same formulation and discusses their results in terms of safety and efficacy.

The medicinal product 'Mexiletine hydrochloride hard capsules' contains the same drug substances, Mexiletine, in the same pharmaceutical form and proposed indications in line with approved formulations in Europe, which are in use in European community since long time, hence safety and efficacy of this formulation has already been established.

The active substance of proposed formulation is Mexiletine.

Mexiletine, 1-(2', 6'-dimethylphenoxy)-2-aminopropane, is a Class IB antiarrhythmic agent, approved for the treatment of ventricular arrhythmias. Structurally and electrophysiologically, mexiletine is similar to lidocaine.



Mexiletine Hydrochloride

Chemical data of Mexiletine hydrochloride

Chemical Data	
Name	Mexiletine Mexiletine hydrochloride
Synonyms	Mexitil
IUPAC Name	1-(2,6-dimethylphenoxy) propan-2-amine (Mexiletine) 1-(2,6-dimethylphenoxy) propan-2-amine hydrochloride (Mexiletine hydrochloride)
Chemical Formula	C ₁₁ H ₁₇ NO (Mexiletine) C ₁₁ H ₁₈ ClNO (Mexiletine hydrochloride)
Molecular Mass	179.263 g/mol (Mexiletine) 215.721 g/mol (Mexiletine hydrochloride)
Identifiers	
CAS No.	31828-71-4 (Mexiletine) 5370-01-4 (Mexiletine hydrochloride)
ATC Code	C01BB02 (antiarrhythmics, Class 1b)
Pubchem	4176 (Mexiletine) 21467 (Mexiletine hydrochloride)

Mexiletine, a local anaesthetic and antiarrhythmic agent structurally akin to lidocaine, effectively suppresses induced ventricular arrhythmias by inhibiting the inward sodium current, thereby reducing the action potential's rate of rise (Phase 0). It decreases the Effective Refractory Period (ERP) in Purkinje fibers, with a more pronounced effect on Action Potential Duration (APD), leading to an increased ERP/APD ratio. While Mexiletine generally does not impact conduction velocity, it may slow conduction in patients with pre-existing abnormalities and can notably depress the sinus rate and prolong sinus node recovery time in individuals with sick sinus syndrome. Notably, Mexiletine has minimal effects on various cardiac parameters such as resting membrane potential, AV conduction velocity, QRS, QT intervals, and more.

When administered orally, Mexiletine reaches peak plasma concentrations within 2 to 4 hours, having a high bioavailability of approximately 90%. Metabolized extensively in the liver by CYP2D6 enzymes, with the involvement of CYP1A2, Mexiletine's major metabolites include p-hydroxymexiletine, hydroxy-methylmexiletine, and N-hydroxymexiletine. The drug's elimination half-life ranges from 5 to 15 hours, with renal excretion responsible for 90% of the dose, including 10% as unchanged drug. Notably, a linear relationship between dose and plasma concentration is observed in the 50 mg to 600 mg dose range.

Mexiletine hydrochloride 100 mg and 200 mg hard capsules

Due to above mentioned pharmacological characteristics of Mexiletine, it is indicated for following (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021):

- 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.

Pharmaceutical form and composition:

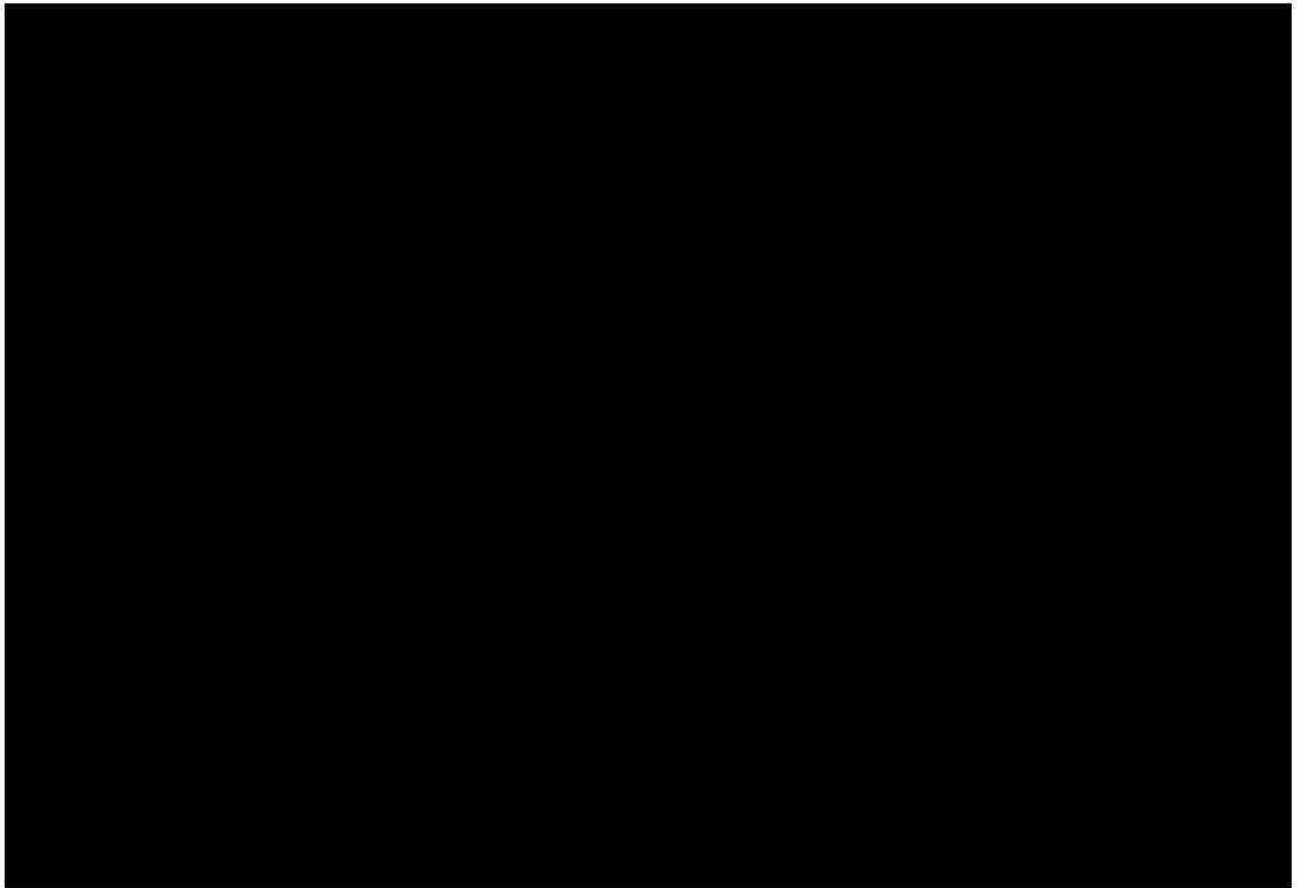
Hard capsules

Each 100 mg and 200 mg hard capsule contains 100 mg & 200 mg of mexiletine hydrochloride, equivalent to 83.10 mg and 166.20 mg of mexiletine respectively.

The proposed indication and dosage of proposed test product are the same as the previously licensed products.

The proposed test product formulation is a dose proportional formulation and composition is same as per UK approved formulation. Moreover, a linear pharmacokinetics relationship between mexiletine dose and plasma concentration has been observed in the dose range of 50 to 600 mg (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

This overview contains all sufficient literature data that support the efficacy and safety of all the proposed strengths of mexiletine. Since Mexiletine is a medicinal product the active substance of which has a 'well-established medicinal use' within the Community for at least ten years, with recognized efficacy and an acceptable level of safety it is possible to replace results of the pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain). As a consequence, the clinical overview only mirrors and summarizes the toxicological and pharmacological well-known properties of the active substance.



2.5.2 Overview of Biopharmaceutics

The Applicant is filing this Marketing authorisation application in UK for Mexiletine hydrochloride 100 mg and 200 mg hard capsules as a “Well Established use application (bibliographic application)”. Accordingly, the Applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community, with recognised efficacy and an acceptable level of safety. In that event, the test and trial results shall be replaced by appropriate scientific literatures, which describe and support clinical part of SmPC. So, the present application is a well-established use application supported by extensive efficacy and safety evidence from literatures rather than clinical study.

Since the composition and proposed indication of the medicinal product Mexiletine hydrochloride hard capsules is same as that of the already approved and registered brands of Mexiletine hydrochloride hard capsules in UK, no new biopharmaceutical studies were deemed necessary on the formulation object of this Application.

The product has been licensed in UK for over more than 10 years as oral capsule for medicinal use. The oral dosage form of Mexiletine is in use globally in clinical practice since long time hence this product is considered as safe and effective for proposed indications.

Furthermore, the drug product manufacture [REDACTED] conducted Bioequivalence studies (Ref. No. BE/19/375 fasting & BE/19/376 fed states) for higher strength (Mexiletine hydrochloride capsules 250 mg) of this product as part of its marketing authorization application of [REDACTED] and the results were satisfactory, meeting all acceptance criteria [Ln-transformed primary PK parameters C_{max}, AUC_{0-t} and AUC_{0-inf} were found within the acceptable BE limits of 80.00% to 125.00% for Mexiletine]. [REDACTED]

[REDACTED]

[REDACTED]

Bridging Study:

To support the application, the applicant (Waymade PLC, UK) also conducted a bridging study, to derive the in-vivo pharmacokinetic data for the test product, Mexiletine 200 mg capsules, through dose adjustment/extrapolation and comparison with available literature data from the public domain. The linearity of mexiletine's pharmacokinetics allows for such adjustment. The findings of this comparison are presented in table below:

Table 1: Comparison of pharmacokinetic data of Total Mexiletine between data from the public domain and results obtained after dose adjustment for Mexiletine 200 mg capsules from BE study [BE/19/375 - fasting conditions]

Source/Reference	AUC _{0-t} (hr*ng/mL)		Cmax(ng/mL)		Tmax (hr)	
	Mean	Range	Mean	Range	Median	Range
	6004.3	3848 - 12910	532.8	325 - 1240	2.00	1.13 - 4.68
	4203.0	NA	342.0	NA	3.17	NA
	3909.0	NA	310.0	NA	3.13	NA
	7273.1	4047 - 11946	448.1	278 - 671	2.33	1.00 - 6.00

NA: Not Available

Table 2: Comparison of pharmacokinetic data of Total Mexiletine between data from the public domain and results obtained after dose adjustment for Mexiletine 200 mg capsules from BE study [BE/19/376 -fed conditions]

Source/Reference	AUC _{0-t} (hr*ng/mL)		Cmax(ng/mL)		Tmax (hr)	
	Mean	Range	Mean	Range	Median	Range
	6004.3	3848 - 12910	532.8	325 - 1240	2.00	1.13 - 4.68
	4311.0	NA	332.0	NA	4.1	NA
	3769.0	NA	297.0	NA	4.8	NA
	4998.6	3769 - 5829	370.6	297 - 442	4.00	2.63 - 4.8
	8173.2	3880 - 12211	545.1	258 - 1065	3.02	1.00 - 5.50

NA: Not Available

The comparison of the pharmacokinetic parameters of total mexiletine with the pharmacokinetic parameters reported in literature indicate the AUC of the proposed product are within the range of literature data. The minor difference in Cmax values could be due to study conduct on different occasions and in different study population. The change in absolute values might also resulted by two different bioanalytical methods used in studies. This type of minor difference is also observed in various reported study findings in literatures. However, it shall be

Mexiletine hydrochloride 100 mg and 200 mg hard capsules

noted that the minor difference in pharmacokinetic parameters will not alter its efficacy and safety of Mexiletine, which is known for wider safety and efficacy margin.

The applicant, Waymade PLC, UK, also performed a comparative study of the most appropriate parameters i.e. ratio of mean values of pharmacokinetic parameters C_{max} and AUC of Mexiletine 200 mg capsules and Mexiletine 250 mg capsules. Results are presented in table below:

Table 3: Comparison of ratio of mean values of pharmacokinetic parameters C_{max} and AUC of waymade's Mexiletine 200 mg capsules with literature data

Source	Condition	C _{max}		AUC		T _{max}		C _{max} (T/R ratio)	AUC (T/R ratio)
		T	R	T	R	T	R		
	Fast	342.0	310.0	4203.0	3909.0	3.17	3.13	1.10	1.08
	Fast	448.1	467.9	7273.1	7575.0	2.33	2.33	0.96	0.96
	Fed	332.0	297.0	4311.0	3769.0	4.1	4.8	1.12	1.14
	Fed	545.1	569.6	8173.2	8468.2	3.02	2.33	0.96	0.97

T: Test product; R: Reference product

Table 4: Comparison of ratio of mean values of pharmacokinetic parameters C_{max} and AUC of waymade's Mexiletine 250 mg capsules with literature data

Source	Condition	C _{max}		AUC		T _{max}		C _{max} (T/R ratio)	AUC (T/R ratio)
		T	R	T	R	T	R		
	Fast	498.5	475.27	5774.6	5603.5	3.00	2.77	1.05	1.03
	Fast	560.2	584.9	9091.4	9468.8	2.33	2.33	0.96	0.96
	Fed	553.0	491.8	7287.2	6840.2	2.65	3.29	1.12	1.07
	Fed	681.3	712.0	10216.45	10585.3	3.02	2.33	0.96	0.97

T: Test product; R: Reference product

The above comparative study confirms that all obtained results are well within acceptance criteria and comparable with results reported in literatures.

Strength Proportionality:

The proposed product is available in two strengths 100 mg and 200 mg. The qualitative and quantitative composition of Mexiletine 100 mg and 200 mg capsules are presented below:

Table 5: Qualitative and Quantitative composition of fill formulation of proposed test product

A large black rectangular box redacting the content of Table 5, which would typically show the qualitative and quantitative composition of the fill formulation for the proposed test product.

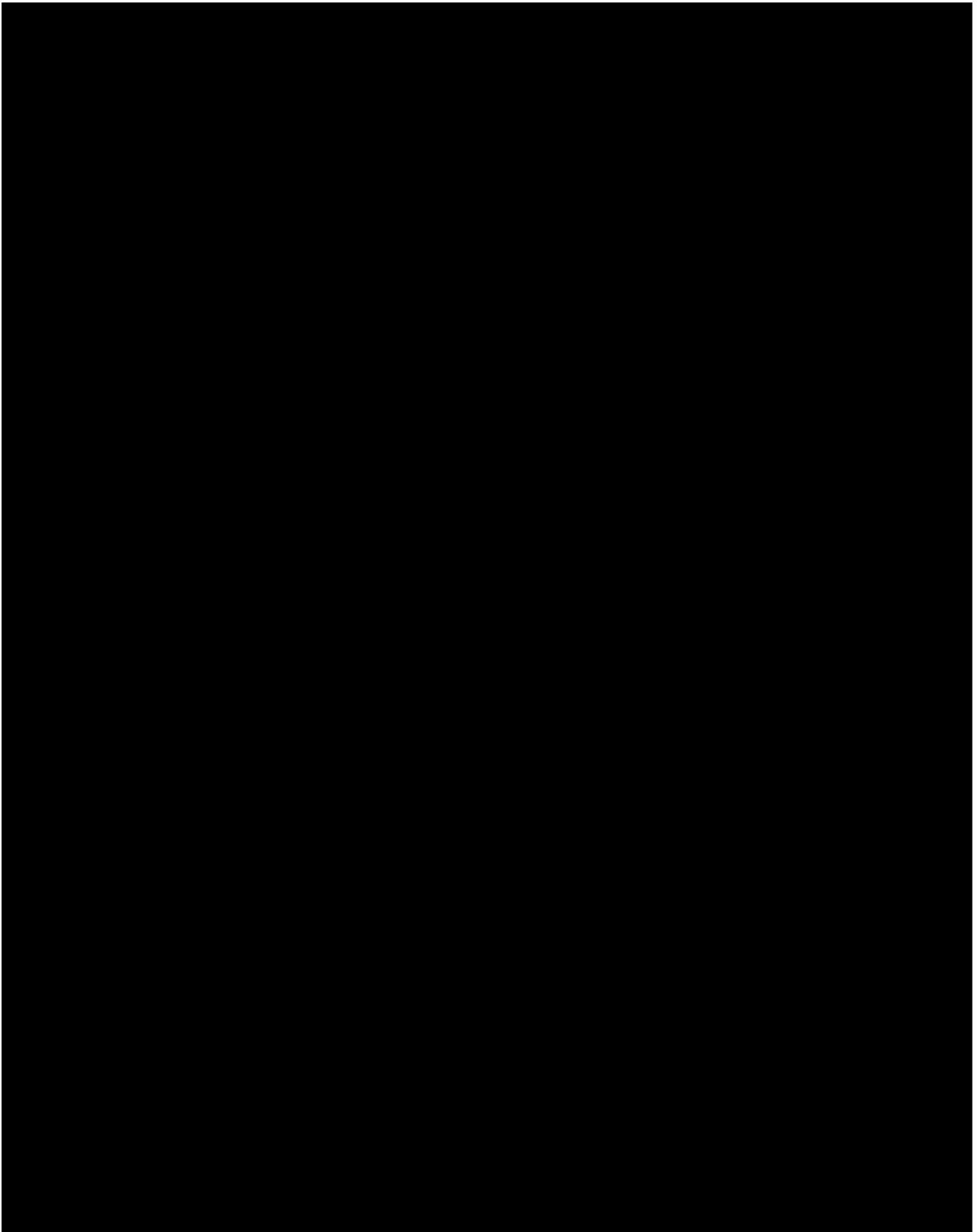
Please refer section 3.2.P.1 of Module 3 for detailed composition including encapsulation stage.

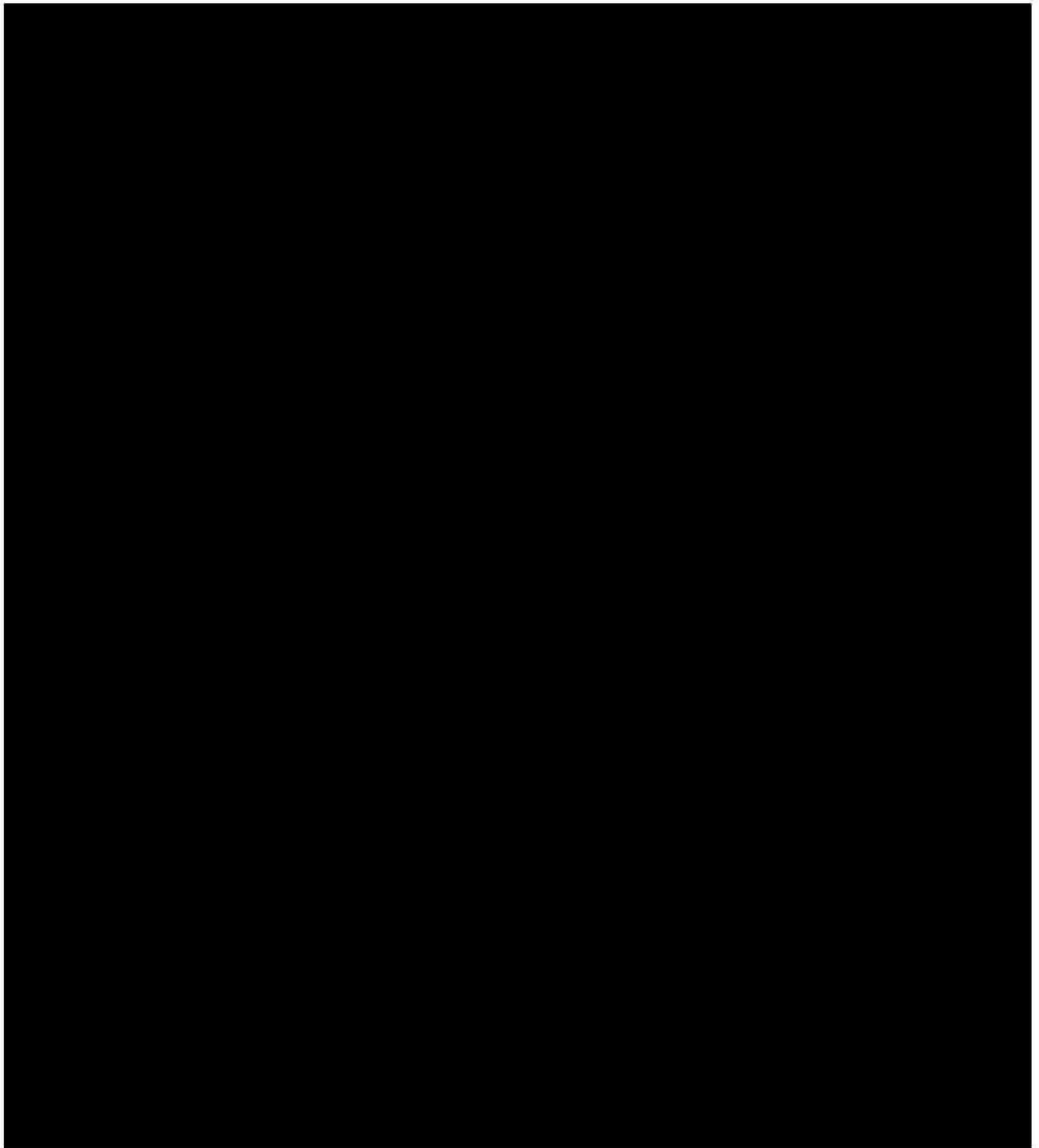
A biowaiver for the additional strengths 100 mg can be applied since the following requirements are met, as set by the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)

- the pharmaceutical products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same,
- the composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths
- appropriate in vitro dissolution data confirm the adequacy of waiving additional in vivo bioequivalence testing (comparative dissolution profile data are presented in Section 3.2.P.2 of Module 3).
- Mexiletine has linear pharmacokinetics.

Since all the above mentioned requirements are met, a biowaiver can be applied for Mexiletine 100 mg capsules.

Linear Pharmacokinetic:





2.5.3 Overview of Clinical Pharmacology

Pharmacodynamics and 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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

Mexiletine does not usually alter conduction velocity, although it may slow conduction in patients with pre-existing conduction abnormalities. In those with preexisting 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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

Mexiletine blocks fast sodium channels in different types of myocytes. The function of these voltage-gated sodium channels is essential in maintaining cardiac rhythm. During phase 0 of the cardiac action potential, sodium influx (INa) into the cardiomyocytes dominates, which in turn allows the cells to reach a depolarized state. Both open and inactivated sodium channels are antagonized at a specific receptor by mexiletine (figure below). This depresses, as a result, excitability and slows conduction predominantly in the ventricular cells. In comparison to other class I drugs, class IB agents detach from the blocked channels more quickly. This translates into a minimal effect at normal heart rates, whereas at faster rates the blocking effect accumulates and causes a marked reduction in the depolarization slope, i.e. positive use dependence. Additionally, the blockade of these sodium channels alters the late sodium influx (INaL) during phase 2 of the cardiac action potential; this diminishes the action potential duration. Cumulatively, the effective refractory period is shortened, yet the ratio of the effective refractory period to action potential duration, i.e. post-repolarization refractoriness, is prolonged. On the other hand, mexiletine exerts a negligible effect on voltage-gated potassium channels



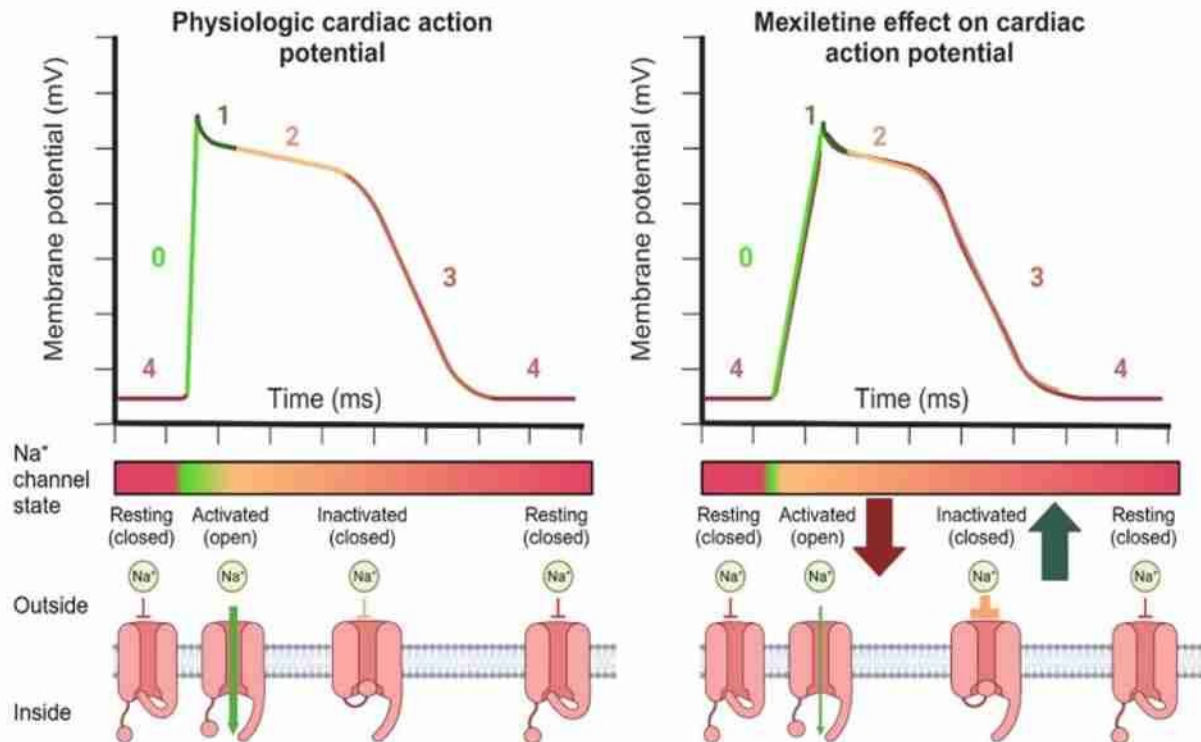


Figure 3: Cellular effects of mexiletine on the cardiac action potential

Experimental studies have proven that ischemic tissue is more sensitive to mexiletine than normally perfused tissue: a well-known phenomenon displayed by lidocaine. Hypoxia induced an increased response to mexiletine in canine Purkinje fibers. In another study by mexiletine was able to effectively suppress ventricular arrhythmias induced by reperfusion in guinea pig isolated hearts. Regarding its influence on hemodynamic parameters, the results of the so far available clinical studies are controversial. One of these studies demonstrated that mexiletine causes, if any, only slight increases in heart rate and blood pressure. This observation could be explained by the anesthetic effect of intravenously administered mexiletine. However, in the majority of these studies, especially those examining patients with ventricular tachyarrhythmias and ischemic heart disease and/or congestive heart failure, mexiletine altered neither the measured hemodynamic variables (heart rate and blood pressure) nor the assessed left ventricular systolic and diastolic functions (left ventricular ejection fraction, stroke volume, and end diastolic volume). Studies support, the lack of a significant effect on the contraction time, myocardial tension index, isometric contraction phase, and cardiac index in patients who received mexiletine for the treatment of ventricular premature contractions was seen. Yet, mexiletine was also able to exert negative inotropic effects, i.e. decrease in the cardiac index, in a small group of patients with severe heart failure [redacted]

In order to assess the hemodynamic impacts of mexiletine, both left ventricular (LV) and right ventricular (RV) ejection fractions (EF) were evaluated using radionuclide ventriculography in a group of 10 patients suffering from left ventricular dysfunction (with LVEF less than 50%). The patient was begun on 300 mg 3 times daily. If arrhythmia persisted, the drug was increased to the highest dosage that was well tolerated. Six patients received 400 mg 3 times daily and 4 patients continued to receive 300 mg 3 times daily. Exercise tests limited by symptoms were also conducted. Observations were made on these patients both prior to and during the course

of treatment with orally administered mexiletine. No substantial alterations were noted in either LVEF (28% vs 27%) or RVEF (46% vs 41%). Furthermore, resting heart rate, duration of exercise, and peak heart rate during exercise remained consistent. Therefore, it can be concluded that in patients with LV dysfunction, oral mexiletine does not significantly influence either LV or RV function [REDACTED]

Changes in cardiac output was determined by continuous-wave Doppler echocardiography during propafenone or mexiletine drug testing in 16 patients while not receiving antiarrhythmic drugs on 2 consecutive days to assess day-to-day variability, as well as while receiving maximally tolerated oral doses of mexiletine (11 patients) and propafenone (9 patients). For mexiletine the starting dose was oral 600 mg/day and the maximum daily dose was oral 900 mg. While receiving propafenone, a drug with moderate negative inotropic activity, peak flow velocity declined by $9 \pm 8\%$ (p less than 0.05), the flow velocity integral (termed stroke distance, representing stroke volume) declined by $8 \pm 11\%$ (p less than 0.10), the rate-corrected stroke distance declined by $9 \pm 8\%$ (p less than 0.02) and the minute distance, representing cardiac output, declined by $10 \pm 12\%$ (p less than 0.05). In contrast, while receiving mexiletine, a drug with minimal negative inotropic activity, none of these parameters changed significantly. Five of 9 patients (56%) treated with propafenone showed a decline in rate-corrected stroke distance exceeding the 95% confidence limit of day-to-day variability, which was ± 13 percent. Two of these 5 patients developed clinical signs of congestive heart failure [REDACTED]

The impact of intravenous mexiletine on hemodynamics was explored in a cohort of 16 patients diagnosed with valvular heart disease, yet showing no signs of heart failure. Among them, a subset of 6 patients received a 150 mg bolus injection, resulting in sustained plasma concentrations within the therapeutic range for over 5 minutes post-administration. This group exhibited a minor but notable elevation in mean pulmonary artery pressure. Furthermore, a comparative analysis between intravenous mexiletine and intravenous saline was conducted in 10 patients, employing a double-blind methodology. No significant variance was observed in the hemodynamic responses between the two substances. Notably, both mexiletine and saline induced a marginal increase in mean pulmonary artery pressure. Overall, the administration of mexiletine, at clinically effective doses, to patients without heart failure did not manifest significant adverse effects on hemodynamics [REDACTED]

The effect of mexiletine [REDACTED] on hemodynamics was investigated in a sample of six patients. Mexiletine was infused at a rate of 10 mg/min for 10 min, after which time the dose was reduced to 6.5 mg/min until the end of the study. Notably, heart rate and cardiac output showed no significant alterations. However, in two patients, systemic arterial pressure experienced a decrease attributed to a decline in peripheral resistance. Assessment of cardiac function through stroke work and pulmonary capillary wedge pressure revealed a reduction in three patients. It's worth noting that all three patients had a current or past history of severe heart failure [REDACTED]

In a randomized study on patients with acute myocardial infarction, Mexiletine was compared to a placebo for its effects on ventricular arrhythmias and cardiac function. Mexiletine, administered as a 2 mg/kg intravenous loading dose followed by 200 mg orally every 6 hours for 24 hours, effectively suppressed ventricular ectopic arrhythmias. While heart rate was slightly lower and pulmonary artery end-diastolic pressure slightly higher in the Mexiletine

group, these differences were not statistically significant. Cardiac index and systemic arterial pressure showed no significant differences between the Mexiletine and control groups

A study on 15 healthy men compared the effects of a 333 mg oral dose of mexiletine to a placebo. Mexiletine, a sodium channel blocker, showed significant impact on muscle velocity recovery cycles (MVRC) measured before dosing and 3 and 5 hours after. It reduced early and late supernormality, indicating decreased muscle fiber action potential velocity after repeated stimulation. This aligns with mexiletine's known effect on muscle membrane excitability by blocking the sodium channel Nav 1.4

The study aimed to assess the effects of antiarrhythmic agents on global left ventricular function during exercise in patients with chronic LV dysfunction. 35 patients with LV ejection fraction less than 45% and ventricular arrhythmias were divided into three groups. Patients underwent baseline and peak exercise equilibrium-gated cardiac-pool scintigraphy to evaluate LV function before and after receiving their assigned antiarrhythmic drug. Disopyramide and pilsicainide groups showed significantly lower exercise LVEF and PER compared to the mexiletine group. Changes in LVEF and PER after drug administration were less in disopyramide and pilsicainide groups compared to baseline. Mexiletine did not significantly impact LV functional parameters during exercise in this patient population. In conclusion, disopyramide and pilsicainide negatively affected global LV function during exercise in patients with chronic LV dysfunction, while mexiletine had no significant impact

The study explored how class I antiarrhythmic drugs affect interatrial conduction time (IACT) in 16 patients. The study found that these drugs prolonged IACT in a use-dependent manner, with different kinetics for each drug. Mexiletine had a fast onset ($1.52 \pm 0.15/n$) and shorter recovery time (203 ± 66 ms), while pilsicainide showed slower onset ($0.050 \pm 0.006/n$) and longer recovery time ($2,930 \pm 569$ ms). This effect is similar to the reduction in cardiac action potential upstroke velocity seen in *in-vitro* studies

The clinical trial showed that late sodium (mexiletine and lidocaine) and calcium (diltiazem) current blocking drugs can reduce heart-rate corrected QT (QTc) prolongation caused by hERG potassium channel blockers (dofetilide and moxifloxacin). Mexiletine and lidocaine decreased QTc by 20 ms, particularly in the J-Tpeak c interval, a marker for late sodium current block. This highlights the potential of late sodium blockers to counteract QTc prolongation from hERG blockers, suggesting J-Tpeak c evaluation adds value beyond traditional QTc assessments

Pharmacokinetics

Absorption and Distribution

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 % (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

A linear relationship between mexiletine dose and plasma concentration has been observed in the dose range of 50 to 600 mg (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

A study examined the pharmacokinetics of S-(+)- and R-(-)-mexiletine, along with their conjugates, in six healthy young volunteers following a single 200 mg oral dose of racemic mexiletine hydrochloride. While the distribution rate constants and elimination half-lives of both enantiomers were similar, the AUC of the S-(+)-enantiomer consistently exceeded that of its counterpart ($P < 0.01$). The mean R/S ratios for unchanged mexiletine in serum and urine were 0.78 ± 0.12 (s.d.) and 0.80 ± 0.21 , respectively. Urinary excretion of mexiletine conjugates was predominantly of the R-(-)-enantiomer, with a mean R/S enantiomeric ratio over 48 hours of 9.65 ± 3.10 . Serum concentrations of the conjugates were measured in three subjects, showing a mean R/S AUC ratio of 2.94 ± 0.48 , and the renal clearance of the R-(-)-enantiomer was significantly higher ($P < 0.02$) than that of the S-(+)-enantiomer [REDACTED]

The study explored serum free and total mexiletine enantiomers kinetics in 12 subjects post 200 mg racemic mexiletine hydrochloride oral intake. Distribution in urine, saliva, and red blood cells was assessed. Peak serum total mexiletine concentration for R-(-)-mexiletine (217 ± 69 ng/ml) exceeded S-(+)-mexiletine (197 ± 56 ng/ml) within 6 hours post-dose. Despite similar absorption, R-(-)-mexiletine concentrations consistently surpassed S-(+)-mexiletine's. *In vitro*, pH influenced stereoselective serum protein binding (30-80% binding at pH 6.3-9.4). Saliva analysis revealed significant differences in area under concentration-time curve ratios. Red blood cell concentrations slightly differed from unity, indicating passive diffusion. The study offers insights into mexiletine enantiomers' pharmacokinetics and distribution across bodily fluids [REDACTED]

The pharmacokinetics of mexiletine enantiomers were assessed in five healthy participants, each receiving a single oral dose of 300 mg racemic mexiletine hydrochloride. Over time, the plasma concentration ratio between R(-) and S(+) enantiomers (R/S) progressively decreased, with mean ratios of 1.37 ± 0.11 at 1 hour and 0.64 ± 0.11 at 48 hours. Similarly, urine R/S ratios were 1.38 ± 0.42 at 1 hour and 0.55 ± 0.12 at 72 hours. The terminal elimination half-life of S(+)mexiletine (11.0 ± 3.80 hours) was significantly longer ($p < 0.05$) than that of the R(-) enantiomer (9.10 ± 2.90 hours). S(+)Mexiletine also exhibited a significantly higher apparent volume of distribution ($p < 0.01$) and renal clearance ($p < 0.05$) compared to R(-)mexiletine. However, there was no significant difference in the apparent oral total drug clearance between the enantiomers. The study concluded that the disposition of mexiletine enantiomers in humans was stereoselective, likely influenced by differences in serum protein binding

The pharmacokinetics of mexiletine were evaluated in 12 healthy volunteers who received oral doses ranging from 100 to 600 mg. While all 12 subjects received doses up to 400 mg, only 11 received the highest dose of 600 mg. Notably, there were no noteworthy alterations in heart rate or blood pressure observed at any dose level. With increasing mexiletine dosage, there was a progressive rise in maximum plasma concentration (as depicted in figure below and table below). However, there were no significant changes noted in clearance or volume of distribution across the various dosage levels. Nonetheless, there were significant differences ($p=0.05$) observed in plasma elimination half-lives between doses, ranging from 7.9 ± 0.6 to 11.3 ± 1.0 hours. These results indicate that the kinetics of mexiletine are linear

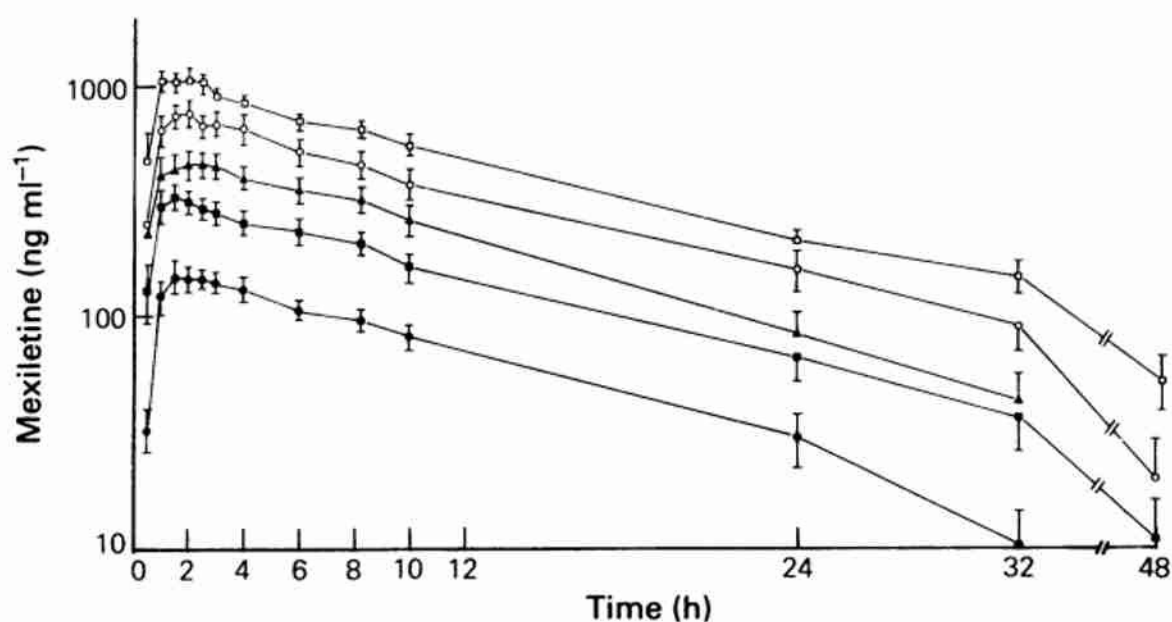


Figure 4: Plasma concentrations of mexiletine (mean $\pm$ s.e. mean ng ml^{-1}) during the 48 h period following oral doses of 100 (●), 200 (■), 300 (▲), 400 (○) and 600 (□) mg mexiletine in each of 12 healthy volunteers

Table 8: Pharmacokinetic parameters of mexiletine after single oral doses of 100, 200, 300, 400 and 600 mg to 12 healthy male subjects. Results are expressed as mean $\pm$ s.e. mean.

Parameter	Parameter value at indicated dose (mg)				
	100	200	300	400	600*
C_{max} (ng ml ⁻¹)	177 $\pm$ 18	381 $\pm$ 41	560 $\pm$ 81	885 $\pm$ 100	1223 $\pm$ 112
Time to C_{max} (h)	1.9 $\pm$ 0.2	1.8 $\pm$ 0.3	2.0 $\pm$ 0.3	2.6 $\pm$ 0.6	1.8 $\pm$ 0.2
k_{el} (h ⁻¹)	0.067 $\pm$ 0.006	0.078 $\pm$ 0.01	0.093 $\pm$ 0.007	0.077 $\pm$ 0.007	0.068 $\pm$ 0.005
$t_{1/2}$ (h)	11.3 $\pm$ 1.0	10.8 $\pm$ 1.2	7.9 $\pm$ 0.6	9.5 $\pm$ 0.7	10.7 $\pm$ 0.8
AUC (ng ml ⁻¹ h)	2511 $\pm$ 324	5094 $\pm$ 785	6870 $\pm$ 1195	11,373 $\pm$ 1714	16,438 $\pm$ 1760
CL (l h ⁻¹)	45.9 $\pm$ 4.6	52.2 $\pm$ 9.7	57.0 $\pm$ 8.2	46.7 $\pm$ 7.8	40.4 $\pm$ 3.8
V (l)	707 $\pm$ 80	695 $\pm$ 91	592 $\pm$ 60	580 $\pm$ 60	591 $\pm$ 43

*Mean of 11 subjects.

The single-dose kinetics of mexiletine (MEX) were investigated in six healthy individuals using three different formulations: a 200 mg intravenous infusion, 400 mg administered via two conventional capsules, and 432 mg in sustained-release dosage forms. Employing a three-compartment open model with a lag time, kinetic parameters were derived from experimental plasma level data. While the mathematical analysis of distribution and elimination processes was based solely on intravenous data, the resulting transfer constants were applied to oral experiments. This approach yielded a common value for plasma elimination half-life ($t_{1/2}$ gamma = 6.34 $\pm$ 1.5 hours). Mean values for total volume of distribution ($V_{d_{tot}}$) and total body clearance (CL_{tot}) were determined as 5.5 l/kg and 10.3 ml/min/kg, respectively. Following capsule administration, peak plasma concentrations (C_{max} = 0.77 microgram/ml) were attained after 2.2 hours, while the sustained-release form resulted in a prolonged, flat concentration profile (C_{max} = 0.34 microgram/ml) peaking at 9.2 hours. Mexiletine demonstrated high bioavailability, nearly identical for both oral formulations: 87.3% for capsules and 78.7% for the slow-release form [REDACTED]

Table 9: Absolute bioavailability of mexiletine in two oral formulations

B%	Subject						$\bar{x}$ (N = 6)
	1	2	3	4	5	6	
Conventional capsule (200 mg)	83.9	69.6	82.7	88.9	88.0	110.5	87.3
Sustained-release form (432 mg)	101.0	46.9	69.9	94.8	71.6	88.2	78.7

In vitro testing assessed mexiletine enantiomers' binding to human serum proteins using samples from five healthy males. Concentrations ranging from 0.2 to 2.0 micrograms/mL of racemic mexiletine were added to each subject's serum. Results showed higher binding for R(-) mexiletine than S(+). No concentration-dependent trends were noted within the therapeutic range, but significant variability in free fractions among individuals was observed. Overall, total binding of the enantiomers was 76% [REDACTED]

In a separate study, healthy subjects received mexiletine intramuscular injections at doses of 50, 100, and 400 mg, and their resulting plasma concentrations were compared with those following a 100 mg intravenous administration. The findings revealed complete bioavailability of mexiletine through intramuscular administration, with dose-linear kinetics observed

In a study, doses of 50 mg (n=3), 100 mg (n=3), 150 mg (n=5), 200 mg (n=6) and 300 mg (n=10) were administered in 27 patients with frequent VPCs. The increase in C_{max} and AUC was dose-dependent, revealing significant correlations between dosage (mg/kg) and C_{max} ($r=0.87$, $p<0.01$) or AUC ($r=0.91$, $p<0.01$)

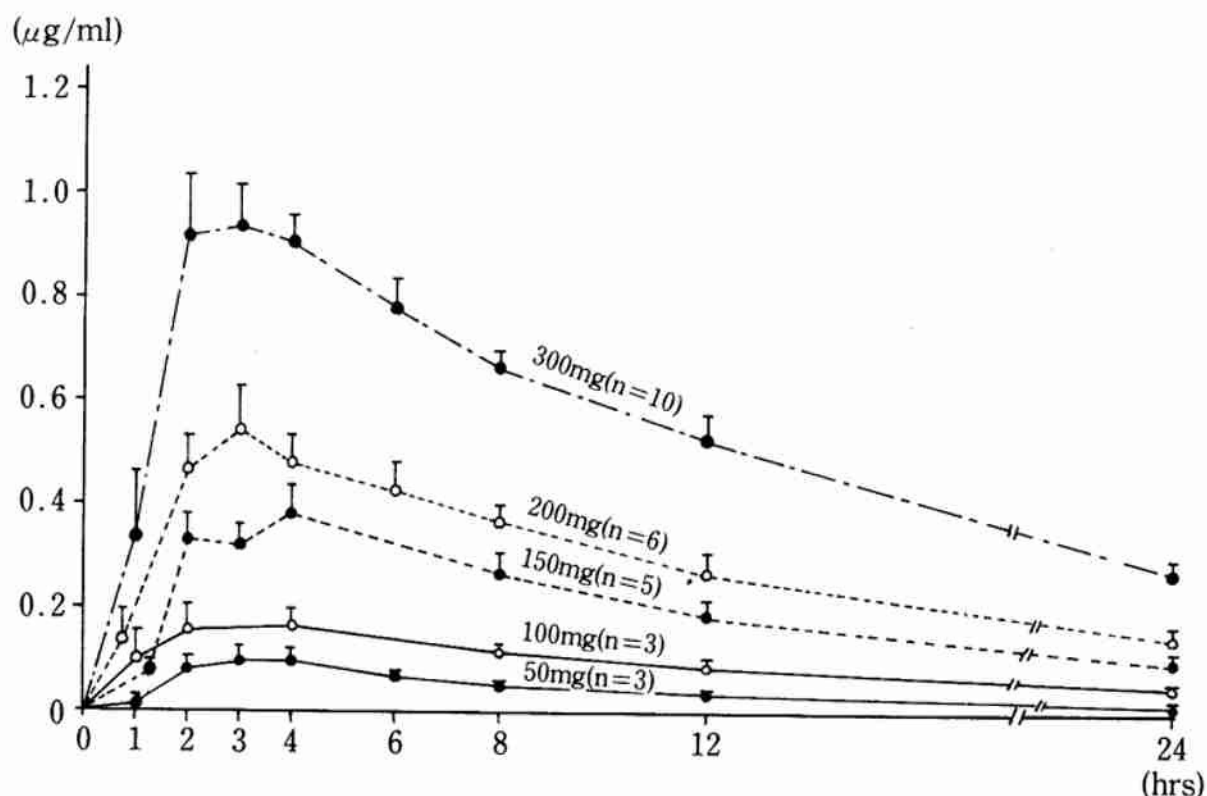


Figure 5: Plasma concentrations of Mexiletine versus time following oral administration

Eight institutionalized Caucasian adult males with uncontrolled seizures received daily doses of 200, 400, 600, or 800 mg of mexiletine capsules four times a day for 7 days, alongside their regular medication. By the second day, serum concentrations of mexiletine significantly increased with the 600 and 800 mg dosages compared to the 200 and 400 mg dosages. However, there were no significant differences between the 200 and 400 mg dosages or between the 600 and 800 mg dosages. Serum concentrations for the 200 and 400 mg dosages were generally below 400 ng/ml, while for the 600 and 800 mg dosages, they ranged from 400 to over 1,100 ng/ml after the first day

Caution is advised when using mexiletine capsules in patients with a history of seizures due to potential increases in serum concentrations with multiple doses.

In a fasting healthy male (100 kg, 188 cm), a 300 mg oral dose of mexiletine hydrochloride was administered, and blood and urine samples were collected. The plasma concentration-time

curve, analyzed with a non-linear least squares computer program, indicated rapid absorption of both enantiomers within 2.5 hours, fitting a two-compartment open model. Terminal elimination half-lives were calculated as 12.1 hours for the R (-) enantiomer and 14.1 hours for the S (+) enantiomer. Notably, the enantiomeric ratio reversed around 8 hours. Similar reversal was observed in urinary excretion at 4.5 hours. The area under the plasma concentration-time curve was 2.04 $\mu\text{g/ml.h}$ for the R (-) enantiomer and 2.24 $\mu\text{g/ml.h}$ for the S (+) enantiomer, calculated by the trapezoidal rule. Cumulative urinary excretion was 8.01 mg for R (-) -mexiletine and 10.46 mg for S (+) -enantiomer, consistent with plasma data

A study determined concentrations of mexiletine enantiomers in the plasma of a subject who received a single oral dose of racemic mexiletine hydrochloride (200 mg). Figure below shows the concentration-time profile for S-(+)-and R-(-)-mexiletine obtained. The elimination half-lives for the S-(+) - and the R-(-)-enantiomers, as calculated from the slope of the terminal linear portion of the curve, were 6.9 and 7.5 h, respectively

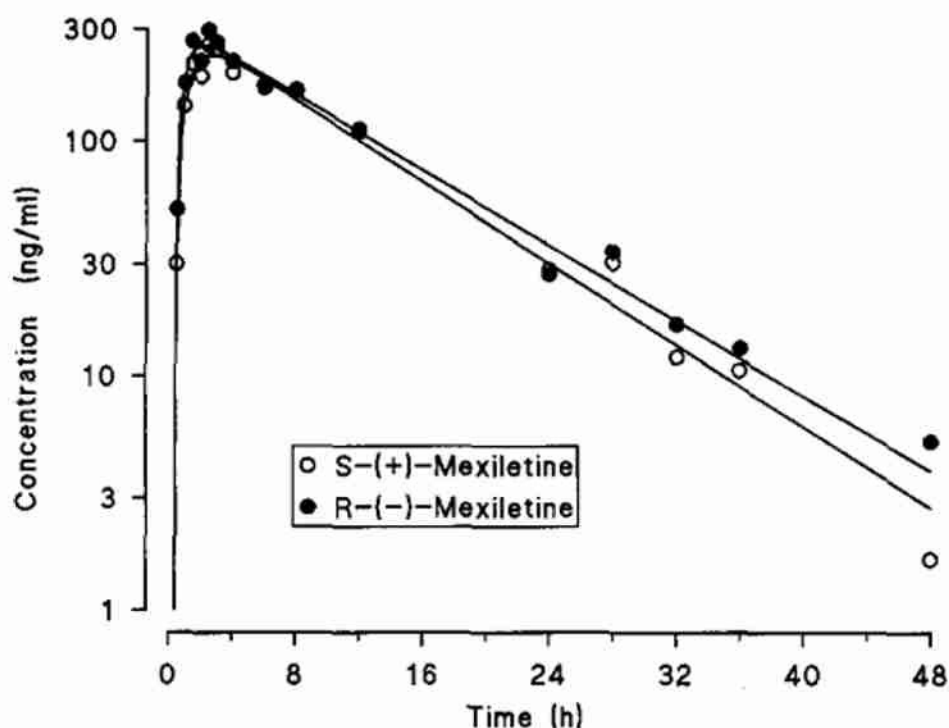


Figure 6: Plasma concentration-time profile of S-(+)-mexiletine and R-(-)-mexiletine obtained after oral administration of 200 mg of RS-mexiletine hydrochloride (Mexitil) to a healthy young volunteer.

The study examined mexiletine kinetics and correlations between serum and saliva levels in five healthy volunteers post-administration of a single oral dose (200 mg). Saliva consistently exhibited higher mexiletine levels than serum, and analysis via the non-linear least squares regression program MULTI revealed a two-compartment model with first-order absorption. Post-absorption, saliva drug concentration correlated well with corresponding serum total or unbound drug levels in four subjects, despite inter-individual variation in the saliva-to-serum

drug concentration ratio and pharmacokinetic parameters, yielding nearly consistent ratios within each individual [REDACTED]

Mexiletine pharmacokinetics were assessed in 59 patients with acute or chronic ventricular arrhythmias. Initially, rapid disappearance from circulation required 500-750 mg within 3 hours to sustain effective plasma concentrations. Subsequently, slow elimination led to rising plasma levels during infusions of 500-1000 mg over 24 hours. Therapeutic and toxic plasma concentrations are outlined below. The minimum therapeutic concentration, determined in 37 patients, ranged from 0.5-2.0 µg/mL, effectively controlling arrhythmias. Lower concentrations were effective for non-acute arrhythmias and digitalis intoxication. Mild toxicity was seen at 0.8-3.0 µg/mL, while severe toxicity occurred at 1.0-4.4 µg/mL. Some patients tolerated concentrations over 5 µg/mL without issue. Oral loading doses of 400-600 mg achieved peak concentrations of 1.0-2.5 µg/mL, with therapeutic levels maintained at 1.0-2.0 µg/mL with 150-300 mg every 6-8 hours. Oral administration showed no cardiovascular toxicity; adverse reactions like nausea and dizziness were rare, mild, and managed by dose reduction [REDACTED]

Table 10: Plasma concentrations of mexiletine in relation to therapeutic and toxic effects

Patients and treatment	No. of patients	Mean minimum therapeutic concentration (µg./ml.) and range	Mean minimum toxic concentrations (µg./ml.) and range	
			Mild toxicity	Severe toxicity
<i>Intravenous</i>				
Acute ventricular arrhythmias:				
Acute myocardial infarction	15	1.1 (0.5-2.0)	1.9 (0.8-3.0)	3.0 (1.0-4.4)
Post-cardiac surgery	1	..	..	4.4
Non-acute ventricular arrhythmias:				
Digitalis toxicity	4	0.7 (0.6-1.2)	*	*
Others	3	0.9 (0.4-1.5)	*	*
<i>Oral</i>	14	0.9 (0.5-1.9)	1.8 (0.9-2.8)	*

* No toxicity encountered.

In a study examining mexiletine's efficacy in preventing arrhythmias in acute myocardial infarction (AMI) patients, pharmacokinetics were investigated. Ninety-nine patients were randomly assigned to receive either mexiletine or a placebo. Upon trial enrollment, 250 mg of mexiletine hydrochloride (Mexitil, Boehringer Ingelheim) or a placebo was infused in 100 ml of 5% dextrose over 30 minutes. Simultaneously, two 200 mg capsules were administered orally. Two hours later, a single 200 mg capsule was given. Ten hours post-infusion commencement, a dosage of 200 mg thrice daily commenced, terminating 42 hours post-

infusion initiation. Mean serum mexiletine concentrations are detailed in table below. Unfortunately, samples from one patient were misplaced in the laboratory. Following the 2nd-hour sample, the total sample count decreased due to premature trial termination. The elimination phase half-life of mexiletine was calculated to be 13.7 ± 7.2 hours (mean $\pm$ standard deviation) [REDACTED]

Table 11: Serum levels of mexiletine in patients with acute myocardial infarction (means $\pm$ sd.) and their frequency distributions

Time (h)	Serum mexiletine ($\mu\text{g ml}^{-1}$)	No. of patients for given mexiletine concentrations			Total
		<0.5 $\mu\text{g ml}^{-1}$	0.5–2.0 $\mu\text{g ml}^{-1}$	> 2.0 $\mu\text{g ml}^{-1}$	
2	0.95 ± 0.46	6	27	1	34
10	0.76 ± 0.27	5	27	–	32
26	0.69 ± 0.28	11	19	–	30
42	0.67 ± 0.38	12	17	–	29
48	0.74 ± 0.34	8	21	–	29
54	0.52 ± 0.28	14	13	–	27
60	0.40 ± 0.23	18	10	–	28

The PK-PD relationship of mexiletine was examined in a study investigating its efficacy in patients with ventricular arrhythmias. Among those with measured mexiletine blood levels, the mean concentration was $0.94 \mu\text{g/dl}$ (range < 0.2 to 2.1). Little correlation between dose and blood levels was observed at doses exceeding 300 mg/day. Among the 33 patients with therapeutic mexiletine blood levels, there was a mean 55% decrease in premature ventricular complexes per 24 hours ($5,732 \pm 1,228$ versus $2,576 \pm 625$, $p < 0.025$), with 13 patients (39%) experiencing a greater than 83% reduction. However, in these responsive patients, four (35%) experienced side effects necessitating drug discontinuation, and one patient suffered sudden death (the same patient previously noted). Thus, among the 33 patients with therapeutic blood levels, 9 (27%) demonstrated drug efficacy without significant side effects, with a mean treatment duration of 14.8 months (range 3.7 to 34.4) [REDACTED]

The study assessed mexiletine's pharmacokinetics in an intravenous efficacy trial, also evaluating a conversion method to oral therapy. Fifteen patients with repetitive ventricular ectopy (13 with ventricular tachycardia) received intravenous mexiletine at 10 mg/min for 30 to 60 minutes. Ventricular ectopy was effectively suppressed with minimal side effects in 10 patients. Oral mexiletine at 10 mg/kg/24 hr was initiated immediately post-intravenous therapy in responders. Plasma mexiletine concentrations at the end of intravenous infusion ranged from 0.4 to 1.5 $\mu\text{g/ml}$. Mean plasma concentrations were $0.8 \pm 0.07 \mu\text{g/ml}$ in responders and $1.4 \pm 0.1 \mu\text{g/ml}$ in non-responders due to protocol-driven higher intravenous doses. Subjects with minor CNS reactions during infusion had the highest plasma concentrations (1.5 and 1.8 $\mu\text{g/ml}$). During oral dosing, four subjects experienced adverse reactions at concentrations of 1.3 to 1.9 $\mu\text{g/ml}$. Trough plasma concentrations in effectively treated subjects ranged from 0.6

to 1.9 µg/ml (mean ± SD = 1.1 ± 0.1 µg/ml), with peak concentrations from 0.8 to 2.2 µg/ml (mean ± SD = 1.5 ± 0.1 µg/ml) [REDACTED]

Metabolism and Elimination

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

The effect of spontaneous changes in urinary pH on renal excretion and plasma concentration of mexiletine was examined during chronic administration of subtherapeutic doses of the drug to healthy volunteers. Significant correlations were found between urinary pH and the plasma concentration and renal excretion of mexiletine. Prediction of plasma mexiletine concentrations suggests that the amount of mexiletine in plasma would increase by more than 50% following a rise in urinary pH similar to that which occurred spontaneously in the subjects. Factors which influence urinary pH should be considered when the dosage of mexiletine is chosen. Extremes of urinary pH may account for some cases of inefficacy of the drug, and for the occurrence of unwanted effects at conventional doses [REDACTED]

In a study with five subjects, mexiletine disposition was assessed under controlled urine pH levels of 5.0 and 8.0. Acidic urine (pH 5.0) showed consistent total plasma clearance (462-497 ml/min) and varied plasma half-life (3.8-9.2 hours, mean 6.7 hours). Alkaline urine (pH 8.0) led to diverse total plasma clearance (239-441 ml/min) and a mean half-life of 9.7 hours (range 7.6-12.7 hours), similar to acidic conditions. Notably, renal clearance of mexiletine decreased significantly with urine alkalinization, affecting total plasma clearance differently among subjects due to varying non-renal clearance. The study also explored the impact of shifting urine pH from 5 to 8 on predicted steady-state plasma mexiletine concentrations during infusion, revealing a range of increases (5-95%, mean 39%). These results emphasize the intricate influence of urinary pH changes on mexiletine disposition, where renal clearance is predictable but overall disposition is affected by individual differences in distribution volume and non-renal clearance [REDACTED]

The disposition kinetics of serum free (unbound) and total mexiletine enantiomers were studied in 12 healthy subjects following oral administration of 200 mg racemic mexiletine hydrochloride. The cumulative amounts of unchanged R(-)- and S(+)-mexiletine in the urine were found to be variable among the 12 subjects with a mean percent urinary recovery of 3.49 +/- 3.35% for R(-)-mexiletine and 3.68 +/- 3.94% for S(+)-mexiletine [REDACTED]

The study identified key cytochrome P450 enzymes responsible for N-hydroxymexiletine formation. Microsomes with high levels of CYP1A2 or CYP2E1 showed the highest rates of N-hydroxymexiletine formation. Antibodies against CYP1A1/1A2 or CYP2E1 inhibited N-hydroxymexiletine formation by about 40% in human liver microsomes. Further experiments demonstrated that furafylline and alpha-naphthoflavone significantly decreased N-hydroxymexiletine formation. Additionally, the formation rate of N-hydroxymexiletine in human liver microsomes correlated strongly with CYP2B6, CYP2E1, and CYP1A2 activity. Although CYP1A2 was identified as a major enzyme involved in N-hydroxymexiletine formation, the findings suggest contributions from other enzymes like CYP2E1 and CYP2B6. [REDACTED]

The study aimed to clarify the role of human CYP1A2 in mexiletine metabolism. Using microsomes from human liver and B-lymphoblastoid cells expressing human CYPs, researchers assessed the contributions of CYP1A2 and CYP2D6 through relative activity factor (RAF) estimation. Results revealed that while mexiletine p- and 2-hydroxylase activities in human liver microsomes were inhibited by certain compounds and correlated with bufuralol 1'-hydroxylase activity, microsomes expressing human CYP1A2 exhibited lower activity compared to CYP2D6. Despite CYP2D6 being the primary enzyme in mexiletine metabolism, CYP1A2 contributed 7–30% to both p- and 2-hydroxylase activities in human liver microsomes. This study confirms the involvement of CYP1A2 in mexiletine metabolism, providing important insights into its metabolic pathways [REDACTED]

Following a 200 mg intravenous dose of mexiletine (MEX) to a healthy volunteer, serum concentrations of MEX and its metabolites p-hydroxymexiletine (p-OHMEX), hydroxymethylmexiletine (OHMeMEX), and hydroxymethylmexiletine-O-glucuronide (OHMeMEX-OL) were measurable over 24 hours, except p-OHMEX-OL was not detected. Peak concentrations were 0.267 µg/mL for p-OHMEX, 0.475 µg/mL for OHMeMEX, and 0.289 µg/mL for OHMeMEX-OL. Estimated elimination half-lives were 8.9 h for MEX, 5.3 h for p-OHMEX, 8.3 h for OHMeMEX, and 8.5 h for OHMeMEX-OL. In 11 patients receiving oral MEX, p-OHMEX-OL was not detected in serum samples [REDACTED]

Table 12: Concentrations of mexiletine and its metabolites in serum of patients during long-term treatment with mexiletine

Patient No.	Daily dose (mg)	Concentration ($\mu\text{g/ml}$)			
		MEX	<i>p</i> -OHMEX	OHMeMEX	OHMeMEX-OL
1	800	1.60	0.025	0.109	0.105
2	800	0.67	N.D. ^a	0.300	0.325
3	600	0.65	0.047	0.085	0.050
4	800	1.34	0.035	0.290	0.095
5	600	0.52	0.084	0.200	0.320
6	600	0.72	0.260	0.023	0.162
7	600	1.43	0.020	0.180	0.170
8	800	1.90	0.030	0.028	0.040
9	800	1.33	0.064	0.140	0.193
10	800	0.95	0.122	0.238	0.154
11	800	0.87	0.405	0.440	0.206

^a Not detected.

The study investigated the impact of different mexiletine concentrations (20-400 μM) on hydroxymethylmexiletine and *p*-hydroxymexiletine production by human liver microsomes (1.4 mg/ml protein). Lineweaver-Burk plots exhibited linear correlations ($r=0.9954$ and $r=0.9937$ for hydroxymethylmexiletine and *p*-hydroxymexiletine, respectively), suggesting monophasic Michaelis-Menten kinetics. Estimated Michaelis-Menten parameters for hydroxymethylmexiletine and *p*-hydroxymexiletine were $K_M=31.8\pm1.8$ and 29.3 ± 0.8 μM , with corresponding V_{max} values of 0.56 ± 0.6 and 0.64 ± 0.8 nmol/mg protein/h

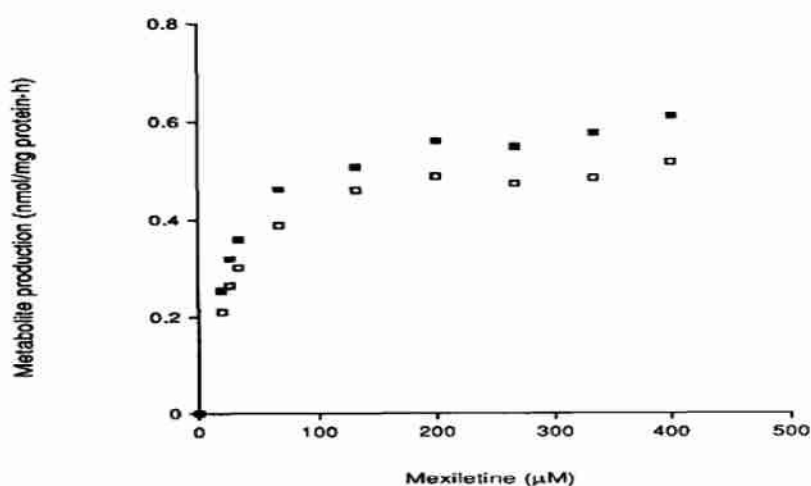


Figure 7: Effect of varying mexiletine concentration (20-400 μM) on the hydroxymethylmexiletine ($\square$) and *p*-hydroxymexiletine ($\blacksquare$) production in human liver microsomes. Protein concentration, 1.4 mg/ml; time of incubation, 240 min.

Pharmacokinetics in special populations

Age

The study examined the impact of age on mexiletine (100-mg oral dose) kinetics by administering a single oral dose of mexiletine hydrochloride to seven elderly and eight young healthy volunteers. In the elderly group, the absorption rate from the gastrointestinal tract was $1.37 \pm 0.51 \text{ hr}^{-1}$, significantly slower than the rate in the young group, which was $2.25 \pm 0.79 \text{ hr}^{-1}$. However, there were no significant differences in elimination half-life between the young group ($12.3 \pm 3.7 \text{ hr}$) and the elderly group ($14.4 \pm 4.5 \text{ hr}$). Similarly, oral clearance was not significantly different between the young group ($10.3 \pm 5.4 \text{ mL/min/kg}$) and the elderly group ($8.5 \pm 2.9 \text{ mL/min/kg}$). Both age groups excreted a comparable amount of mexiletine in urine within 48 hours post-dose, representing less than 5% of the administered dose. Consequently, the study concludes that age-related changes in mexiletine kinetics do not have clinical significance during chronic drug administration [REDACTED]

Race

The study aimed to evaluate mexiletine clearance in a Japanese population and clarify the roles of CYP2D6 and CYP1A2 in mexiletine disposition. In this investigation, serum and urinary concentrations of mexiletine and its metabolites were determined, and mexiletine clearances were estimated in 334 inpatients receiving mexiletine therapy. Results revealed that while interindividual variation in mexiletine clearance was minor, the impact of age on mexiletine clearance was noteworthy. Specifically, mexiletine clearance was found to be lower in patients diagnosed with dilated cardiomyopathy (DCM) compared to those with other diagnoses (Non-DCM). Approximately half of the urinary metabolites consisted of p-hydroxymexiletine (POH) and 2-hydroxymexiletine (OHMEX), with most POH being conjugated and less than one-third of OHMEX being conjugated. Although no significant differences in POH and OHMEX were observed between DCM and Non-DCM patients, a trend towards increased conjugation pathways in DCM patients was noted. In conclusion, the study highlighted minimal interindividual variation in mexiletine clearance, with age exerting a significant influence on clearance in Non-DCM patients. Additionally, a notable disparity in mexiletine clearance was evident between patients with DCM and those without [REDACTED]

Genetic Polymorphism

A study explored how debrisoquine polymorphism and low-dose quinidine, a cytochrome P450IID6 inhibitor, affect mexiletine disposition. Fourteen volunteers (10 extensive metabolizers [EM], 4 poor metabolizers [PM]) received mexiletine alone and with quinidine. PM had lower clearance rates of mexiletine and its metabolites than EM. Quinidine reduced mexiletine clearance and prolonged half-life in EM. It also decreased metabolic clearance of certain mexiletine metabolites in EM, correlating with their debrisoquine metabolic ratio. This highlights the significant impact of cytochrome P450IID6 modulation on mexiletine disposition [REDACTED]

A study investigated how the CYP2D6*10 allele affects MX pharmacokinetics in Japanese individuals. Subjects with different genotypes (*1/*1, *10/*10, and *5/*10) received a single 200-mg dose of MX. Results showed that carriers of the CYP2D6*10 allele exhibited higher

MX levels and decreased clearance. Those with *5/*10 genotype had significantly increased MX levels. Overall, the CYP2D6*10 allele significantly impacts MX pharmacokinetics in this population

A study explored CYP2D6*10's impact on PHM and HMM formation using human liver microsomes of known genotypes (*1/*1, *1/*10, *10/*10). Compared to *1/*1 microsomes, *1/*10 and *10/*10 showed reductions exceeding 50% and 85% in PHM and HMM formation. This suggests significant impairment in mexiletine metabolism, particularly PHM and HMM production, in both heterozygous and homozygous carriers of CYP2D6*10

Hepatic Impairment and Renal Impairment

Cirrhosis's impact on mexiletine pharmacokinetics was studied in six cirrhotic patients and six healthy controls given a 200 mg single i.v. dose. Mexiletine's distribution wasn't significantly affected by cirrhosis, with similar values for V_1 and V_{ss} . However, elimination was significantly slower in cirrhotic patients, with total clearance averaging only 28% of the control value. The elimination half-life was 2.9 times longer in cirrhotics. Mexiletine's plasma protein binding showed no significant difference between cirrhotic patients and healthy controls. There was a significant correlation between the elimination half-lives of mexiletine, as well as between the total clearances

Table 13: Model independent pharmacokinetic parameters obtained after intravenous administration of mexiletine^a to 6 patients with cirrhosis of liver and 6 healthy volunteers

Parameter	Cirrhotic patients	Healthy volunteers	<i>p</i>
AUC [mg·h·l ⁻¹]	21.6 ± 6.0 ^b	6.25 ± 0.91	<0.05
Cl _p ml/min/kg	2.31 ± 0.32	8.27 ± 1.23	<0.01
t _{1/2α} [h]	0.60 ± 0.18	0.22 ± 0.10	N.S.
t _{1/2β} [h]	28.7 ± 4.0	9.9 ± 1.6	<0.01
Protein ^c [%]	51 ± 3	45 ± 4	N.S.

^a dose 200 mg of mexiletine HCl; ^b mean ± SEM; ^c protein bound fraction

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

In a study of 82 patients with ventricular arrhythmias and liver, renal, or heart issues, researchers examined the pharmacokinetics of oral mexiletine at a daily dose of 600 mg. Patients were divided into groups: control (n = 51), liver cirrhosis (n = 9, Group C), renal insufficiency (n = 14, Group A), or heart failure (n = 8, Group B). Patients aged 22 to 78 years received oral mexiletine three to five times daily for about 4 weeks. The study found a correlation between plasma concentration and mexiletine daily dose. Among the patients

receiving 600 mg daily (n=19), 800 mg (n=21), or 1000 mg (n = 11), mean plasma levels varied significantly, ranging from 0.63 µg/ml (600 mg daily dose) to 0.94 µg/ml (800 mg daily dose, $P < 0.01$) and 1.29 µg/ml (1000 mg daily dose, $P < 0.01$). Plasma concentrations in the control group and patients with renal insufficiency (Group A) or heart failure (Group B) did not differ significantly with a 600 mg daily dose. However, patients with liver cirrhosis (Group C) had significantly higher plasma levels (mean 2.21 ± 0.94 µg/ml) compared to the control group ($P < 0.01$) [REDACTED]

A study evaluated the pharmacokinetics of mexiletine in 14 subjects with renal failure, including 5 on dialysis. Subjects received a single 200 mg dose, and blood samples were analyzed for mexiletine levels. The elimination half-life was 18.9 ± 7.4 hours, and oral clearance was 378 ± 109 ml/min. These parameters did not correlate with creatinine clearance. For dialysis patients, drug exposure was not significantly different during or between dialysis sessions. The study concluded that mexiletine dosing adjustments are unnecessary in patients with creatinine clearance ≥ 10 ml/min or on dialysis, and supplemental doses after dialysis are unlikely needed. Mexiletine can be administered without dose modifications in renal impairment [REDACTED]

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

Cardiac failure

A study involving 584 inpatients, 210 with congestive heart failure (CHF) and 374 without CHF, examined mexiletine clearance. Among CHF patients, those with more severe symptoms (NYHA class III-IV) had significantly lower clearance compared to those with milder symptoms (NYHA class I-II) and those without CHF. Mexiletine clearance was 50% lower in NYHA class III-IV patients (mean CL/F ratio of 0.195 L/h/kg) compared to non-CHF patients (mean CL/F ratio of 0.393 L/h/kg). This suggests that CHF presence and severity affect mexiletine clearance, necessitating dosage adjustments and close monitoring for CHF patients on mexiletine therapy [REDACTED]

Drug interactions

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

In a study of 14 patients with ventricular tachycardia, the study examined the effects of monotherapy and combination therapy with mexiletine (MEX) and quinidine (Q) on cardiac function. MEX was administered at 621 mg/day with serum levels of 3.4 µM/L, and Q at 1573 mg/day with serum levels of 8.3 µM/L during monotherapy. In combination therapy, MEX was given at 636 mg/day with serum levels of 3.3 µM/L, and Q at 1643 mg/day with serum levels of 9.5 µM/L. No significant changes were observed in left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), or wall motion score (WMS) with either monotherapy or combination therapy. Exercise performance and ventricular function remained unaffected in patients receiving combination therapy, suggesting that MEX-Q combination therapy does not adversely impact ventricular function in patients with ventricular tachycardia

In a study of 14 patients with sustained ventricular tachycardia, the combination of mexiletine (150 mg three times/day) with a class IC antiarrhythmic agent (encainide, propafenone, or flecainide) was assessed. Mexiletine was administered orally to 13 patients and intravenously to one. After treatment initiation, one patient's ventricular tachycardia became noninducible, while another experienced arrhythmia aggravation. In the remaining 12 patients, ventricular tachycardia remained inducible, but the average cycle length increased insignificantly. Combination therapy did not lead to additional ECG changes compared to monotherapy. However, one patient developed sinus and atrioventricular node dysfunction, which resolved upon reducing the class IC drug dose. Another patient experienced mild congestive heart failure, which resolved with a decrease in propafenone dose. Overall, nine patients with significant rate slowing were discharged on the combination therapy without side effects. During an average follow-up of 22 months, seven patients continued the treatment without arrhythmia recurrence or adverse effects

Torsades de pointes has been observed when mexiletine is given together with amiodarone

Electrophysiological interactions between mexiletine and propafenone were studied in fifteen healthy volunteers, including 8 extensive metabolizers and 7 poor metabolizers of CYP2D6. Participants received oral doses of mexiletine 100 mg twice daily from day 1 to day 8 and propafenone 150 mg twice daily from day 5 to day 12. Interdose studies were conducted at steady-state on mexiletine alone (day 4), mexiletine plus propafenone (day 8), and propafenone alone (day 12). Two hours after dosing, QRS intervals were lower during administration of mexiletine alone compared to propafenone alone or propafenone plus mexiletine ($P < .05$). Moreover, RR intervals at the expected peak plasma concentration of the drugs were longer, whereas QTc intervals were shorter compared with the two other times measured ($P < .05$). CYP2D6 phenotype and smoking status minimally affected these effects. Overall, all changes in electrocardiographic parameters were of minor amplitude in all groups of subjects, indicating subtle effects of the drug interactions

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

A study examined the effect of diamorphine on the pharmacokinetics of mexiletine in 240 high-risk patients with acute myocardial infarction. Patients receiving mexiletine had lower mean plasma levels if they had also received diamorphine compared to those who did not. In the diamorphine group, administering intravenous metoclopramide before the oral mexiletine dose partially reversed the reduction in 3-hour plasma levels, though this was not statistically significant. Metoclopramide did not affect mexiletine levels in patients who had not received diamorphine. These findings suggest diamorphine can significantly reduce mexiletine concentrations, and metoclopramide may help mitigate this interaction [REDACTED]

A preliminary study found that mexiletine absorption was impaired in Coronary Care Unit patients with myocardial infarction who received narcotic analgesics. Patients with myocardial infarction had significantly lower mean plasma mexiletine concentrations compared to those without infarction. Furthermore, patients without infarction who received narcotics also had lower concentrations than those who did not. Due to the small number of infarction patients not given narcotics, no statistical comparisons were made within that group. Notably, 66% of patients with myocardial infarction failed to reach the minimum therapeutic plasma mexiletine level of 1 µg/ml by 3 hours. These findings suggest that the concomitant use of narcotic analgesics can significantly reduce mexiletine absorption, potentially compromising therapeutic efficacy in high-risk cardiac patients [REDACTED]

Administration of a commercially available antacid preparation containing magnesium-aluminiumsilicate hydrate 1 hour prior to a single 400mg oral dose of mexiletine to 10 volunteers resulted in a prolongation of the t_{max} ($1.7 \pm 0.7h$ to $2.9 \pm 1.0h$). Other pharmacokinetic parameters of mexiletine (C_{max} , AUC and absorption $t_{1/2}$) were unaffected. The authors concluded that the prolongation in t_{max} might be explained by a delay in gastric emptying [REDACTED]

Effects of pretreatment with intravenous metoclopramide 10mg and atropine 0.6mg, both separately and combined, on the absorption rate and relative oral bioavailability of mexiletine 400mg were investigated in 8 healthy volunteers. The t_{max} was increased by atropine (1.97 to 3.32h) and reduced by metoclopramide (1.97 to 1.03h). No significant changes in t_{max} were noted when atropine and metoclopramide were administered together. Atropine pretreatment was also associated with a significant reduction in the C_{max} of mexiletine (1.45 to 1.17 mg/L). No alteration in this concentration was observed following administration of either metoclopramide or the combined drugs. The $t_{1/2\beta}$ was reduced only with atropine pretreatment (9.49 to 8.02h). Neither of the drugs had an effect on the AUC of mexiletine, which indicates that the bioavailability of this antiarrhythmic agent was not affected [REDACTED]

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021)

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

In a study with six healthy Japanese men, the study explored the interaction between fluvoxamine and mexiletine. When taken alone, mexiletine showed an area under the concentration-time curve (AUC) of 6.70 ± 3.21 microg x h/mL and a peak concentration (C_{max}) of 0.536 ± 0.164 microg/mL. However, when fluvoxamine was administered for seven days prior to coadministration with mexiletine, the AUC increased to 10.4 ± 4.85 microg x h/mL and the C_{max} rose to 0.623 ± 0.133 microg/mL. This suggests a significant interaction, highlighting the need for careful monitoring when combining mexiletine with fluvoxamine

The study aimed to explore whether the potential inhibition of CYP1A2 by ciprofloxacin would impact the stereoselective disposition of mexiletine. Nineteen healthy men, including both smokers and nonsmokers, were administered a single 200-mg oral dose of racemic mexiletine hydrochloride on two occasions: once alone and once concomitantly with ciprofloxacin 750 mg BID (administered starting 3 days before and up to 2 days after mexiletine). Blood and urine samples were collected for 48 hours to derive pharmacokinetic parameters. The findings revealed that smokers exhibited higher total clearances of both R-(-)- and S-(+)-mexiletine compared to nonsmokers, indicating increased clearance of mexiletine associated with heightened CYP1A2 activity. Conversely, the administration of ciprofloxacin led to a marginal decrease in R-(-)- and S-(+)-mexiletine clearances, primarily due to a reduction in mexiletine's nonrenal clearance. These results confirm the involvement of CYP1A2 in the overall clearance of mexiletine, as evidenced by the increase in nonrenal clearance in smokers and its reduction during combined ciprofloxacin administration

In a study, fifteen healthy volunteers (8 extensive metabolizers, 7 poor metabolizers of CYP2D6) took oral mexiletine and propafenone. Propafenone notably reduced oral clearances of R-(-)-mexiletine (from 41 ± 11 L/h to 28 ± 7 L/h) and S-(+)-mexiletine (from 43 ± 15 L/h to 29 ± 11 L/h) in extensive metabolizers, eliminating differences between metabolizer groups. It also substantially reduced partial metabolic clearances of mexiletine in extensive metabolizers, while having minimal impact on poor metabolizers. Notably, propafenone's pharmacokinetic parameters remained unchanged during concurrent administration with mexiletine

A study investigated the urinary elimination of mexiletine and its metabolites before and after quinidine treatment. All subjects were extensive metabolizers for debrisoquine. The key findings were that the total recovery of mexiletine and metabolites was significantly reduced after quinidine pretreatment, and quinidine markedly inhibited the elimination of the major mexiletine metabolites, PHM and HMM. The study concludes that low-dose quinidine significantly impacts the elimination of mexiletine's major metabolites, PHM and HMM, likely decreasing the overall elimination of the parent drug

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021)

The effects of omeprazole on the pharmacokinetics of a single oral dose of mexiletine 200mg were studied in 9 male Japanese volunteers. In this study, the concentrations and CL/F of mexiletine were not altered after 7 days of administration of omeprazole 40mg daily. Moreover, no measurable differences were noted in the C_{max} , K_a , V_d , $t_{1/2\beta}$ and AUC. In brief, the pharmacokinetics of mexiletine were not altered during the concomitant administration of omeprazole [REDACTED]

Pharmacokinetic interaction of phenytoin and mexiletine in 6 healthy volunteers was studied. Each volunteers received a single 400mg oral dose of mexiletine before and after a 7-day pretreatment with phenytoin 300mg daily under conditions of controlled urinary pH. A significant decrease in the area under the plasma concentration-time curve was observed after phenytoin administration (17.67 ± 6.21 to 8.01 ± 3.64 , $\mu\text{g ml}^{-1} \text{ h}$, $P < 0.003$). This was the result of enhanced clearance of mexiletine as reflected in a decrease in the half-life of elimination (17.2 ± 5.26 to 8.4 ± 4.17 h, $P < 0.02$). Approximate linearity of the β -phase of all curves was reflected by correlation coefficients ranging from 0.94 to 0.99 with a mean of 0.965 (s.d. 0.017) [REDACTED]

Effect of rifampicin treatment on the kinetics of mexiletine was studied. In this study, each of the eight healthy volunteers received a single oral dose of the new antiarrhythmic agent, mexiletine hydrochloride, at 400 mg. This dosage was administered both before and after a ten-day treatment regimen with rifampicin at 300 mg b.i.d. The study revealed that while the absorption and distribution of mexiletine remained unchanged after rifampicin treatment, its elimination half-life decreased significantly from 8.5 ± 0.8 hours to 5.0 ± 0.4 hours ($p < 0.01$). Furthermore, its nonrenal clearance notably increased from 435 ± 68 ml/min to 711 ± 101 ml/min ($p < 0.01$). Although the mean renal clearance of mexiletine did not exhibit any change, it displayed an exponential correlation with urinary pH. The quantity of unchanged mexiletine excreted in urine over two days decreased from 32 ± 7 mg to 18 ± 3 mg ($p < 0.01$). Additionally, the half-life of antipyrine also decreased significantly from 11.8 ± 0.4 hours to 5.5 ± 0.3 hours, with its clearance increasing from 40 ± 3 ml to 74 ± 3 ml/min ($p < 0.01$). Notably, there was a significant positive linear correlation ($p < 0.05$) between the half-lives and clearances of both antipyrine and mexiletine. Moreover, clearances were positively correlated with serum gamma-glutamyl transpeptidase levels. These findings underscore the necessity for dosage adjustment of mexiletine when initiating or discontinuing enzyme-inducing drugs during therapy [REDACTED]

Cigarette smoking may increase the total clearance of mexiletine. Mexiletine dose may need to be adjusted in smokers (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

The study explored how cigarette smoking affected the kinetics of a 200 mg oral dose of the antiarrhythmic drug mexiletine in healthy subjects. Smoking didn't impact absorption or distribution but significantly reduced the drug's elimination half-life from 11.1 ± 3.4 to $7.2 \pm$ [REDACTED]

Module 2.5

1.8 hours, with a lesser effect on clearance. It selectively induced the conjugation of mexiletine with glucuronic acid and aliphatic hydroxylation to yield hydroxymethylmexiletine, while leaving the formation of p-hydroxymexiletine unaffected [REDACTED]

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

Mexiletine (200 mg every 8 hours) significantly reduced the plasma clearance of theophylline in both male (from 32.3 +/- 2.6 to 19.3 +/- 1.3 ml/kg per hour) and female (from 33.5 +/- 2.6 to 17.9 +/- 1.0 ml/kg per hour) nonsmokers after 5 days of treatment. Elimination half-life was prolonged by 74% in males and 103% in females. Mexiletine also decreased formation of all theophylline metabolites, particularly impacting demethylation pathways. This highlights mexiletine's potent inhibition of theophylline metabolism, suggesting the need for up to a 50% reduction in theophylline dosage to prevent toxicity risk when co-administered [REDACTED]

In a study with eight healthy men investigated how mexiletine affected theophylline levels. Participants received theophylline every 12 hours for 9 days and mexiletine for five doses starting on day 6. Mexiletine increased theophylline levels, with mean predose levels rising from 8.1 +/- 0.1 to 13.4 +/- 0.6 micrograms/ml, and AUC₀₋₁₂ from 96.8 +/- 9.1 to 160.2 +/- 3.7 micrograms/ml.hr. Plasma clearance decreased from 44.7 +/- 5.1 to 25.4 +/- 1.2 ml/hr with mexiletine, which also reduced theophylline metabolites by 60%. Levels returned to normal after stopping mexiletine, indicating the need for monitoring when combining these drugs [REDACTED]

Plasma concentrations of lidocaine, its major metabolites, and mexiletine were measured in a patient with dilated cardiomyopathy. Plasma lidocaine concentrations increased significantly when the oral dose of mexiletine was increased. This pharmacokinetic interaction was not attributable to a metabolic interaction as evaluated by plasma lidocaine metabolites concentrations. A strong displacing effect of mexiletine on the binding of lidocaine to phosphatidylserine was observed *in vitro*. A drug interaction derived from the displacement of lidocaine from tissue binding sites by mexiletine that resulted in the increased plasma lidocaine concentrations was shown [REDACTED]

A study examined the impact of mexiletine, a CYP1A2 inhibitor, on the pharmacokinetics and pharmacodynamics of tizanidine in 12 healthy participants. Coadministration of mexiletine significantly increased tizanidine's peak concentration, area under the curve, and half-life compared to tizanidine alone. Mexiletine also enhanced the reduction in systolic and diastolic blood pressure after tizanidine administration. In a retrospective survey, 4 out of 15 patients receiving the combination experienced tizanidine-related adverse effects. These findings

indicate that mexiletine can substantially increase tizanidine exposure and potentiate its pharmacodynamic effects, warranting close monitoring for adverse events when these medications are used concurrently [REDACTED]

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

Mexiletine use slowed caffeine elimination. In healthy volunteers, caffeine clearance dropped from 126 ± 15 ml/min to 54 ± 4 ml/min when taken with mexiletine, while its elimination half-life increased from 246 ± 25 min to 419 ± 28 min, and the volume of distribution decreased from 43 ± 2 L to 32 ± 2 L—significant differences ($p < 0.05$). In patients on long-term mexiletine treatment, caffeine clearance dropped to 37 ± 16 ml/min with a half-life of 878 ± 137 min, but increased to 71 ± 12 ml/min with a half-life of 330 ± 46 min after stopping mexiletine—both differences significant ($p < 0.05$). This suggests mexiletine may contribute to caffeine retention, potentially explaining some of its side effects [REDACTED]

The study examined potential interactions between mexiletine, an antiarrhythmic agent, and 14 psychotropic drugs by assessing their effects on mexiletine metabolism in human liver microsomes. Fluoxetine, sertraline, and desipramine competitively inhibited mexiletine metabolism, while thioridazine and paroxetine exhibited mixed-type inhibition. Predicted changes in mexiletine clearance were 2.4 for paroxetine, 5.5 for fluoxetine, 1.1 for sertraline, 2.8 for desipramine, and 2.2 for thioridazine. Paroxetine also showed mechanism-based inactivation of mexiletine metabolism. These findings suggest possible clinically significant interactions between mexiletine and paroxetine, fluoxetine, desipramine, and thioridazine when used together [REDACTED]

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

Concomitant administration of mexiletine with warfarin may increase the risk of bleeding (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021)

Conclusion

This is an application according to Article 10a well-established use.

The basic pharmacokinetic and pharmacodynamics parameters of Mexiletine are fairly well described in the provided literatures. The above mentioned details about the pharmacodynamics and pharmacokinetics of active ingredient and formulation from various published literatures and approved labels of similar formulation support the well-established use of Mexiletine.

2.5.4 Overview of Efficacy

Mexiletine hydrochloride 100/200 mg hard capsules is indicated for (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021):

- 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.

In a study of 108 patients with chronic ventricular arrhythmias, Mexiletine was tested. 83 had recurrent ventricular tachycardia, 72 were resistant to standard therapy, and 25 had experienced ventricular fibrillation. The study had four phases: baseline monitoring, acute testing with Mexiletine, efficacy assessment, and long-term maintenance. Results showed Mexiletine suppressed ectopic activity in 65% at rest and 58% during exercise. 65.4% showed arrhythmia control in monitoring, with 66.2% during exercise; 60% met criteria in both. In long-term use, 31 patients continued Mexiletine for an average of 12.6 months, maintaining suppression. Mexiletine was effective and well-tolerated in patients resistant to standard drugs

In a double-blind trial the antiarrhythmic effect of oral mexiletine (200-250 mg every 8 h) was investigated in 344 patients judged to be at high risk after acute myocardial infarction. The numbers of patients with ventricular ectopic complexes were similar in the mexiletine and placebo groups at each point of analysis. At 1 month fewer patients in the mexiletine group had couplets and multiform ventricular ectopic beats, but at 3 months the difference was not significant. The hourly average number of ventricular ectopic complexes was significantly reduced by mexiletine at both 1 month and 3 months. Thus mexiletine reduced the prevalence of ventricular arrhythmias in a high-risk group of patients with recent myocardial infarction

The study aimed to evaluate the efficacy of mexiletine in preventing arrhythmias (abnormal heart rhythms) in patients with acute myocardial infarction (AMI, or heart attack). A total of 99 patients were randomly assigned to receive either mexiletine or a placebo treatment. The treatment protocol involved an initial intravenous (IV) loading dose of 250 mg of mexiletine, followed by an oral dose of 400 mg and another 200 mg oral dose two hours later. Thereafter, patients received 200 mg of mexiletine three times a day for up to 42 hours. Continuous electrocardiographic (ECG) recordings were analyzed to detect arrhythmias occurring within 48 hours. The study found that mexiletine treatment significantly reduced the incidence of various types of arrhythmias compared to the placebo group. Fewer patients in the mexiletine group experienced accelerated idioventricular rhythm (AIVR), runs of ventricular premature beats (VPBs), ventricular tachycardia, and R on T beats (a specific type of arrhythmia). Additionally, the mexiletine group had fewer total VPBs and fewer hours with occurrences of AIVR, runs, and R on T beats. The study concluded that combined intravenous and oral mexiletine prophylaxis effectively suppressed repetitive ventricular tachyarrhythmias (rapid and irregular heart rhythms) and R on T beats in patients with acute myocardial infarction

Table 14: Number of ventricular arrhythmias observed in patients with myocardial infarction

Type of arrhythmia	No. of arrhythmias		P*
	Mexiletine group (n=35)	Placebo group (n=38)	
All VPBs	19815	33752	<0.05
Hours with multiform VPBs	198	324	n.s.
Couplets	154	368	n.s.
Hours with AIVR	47	100	<0.05
Runs	31	133	<0.01
VTs	2	15	n.s.
RonT	32	175	<0.05

*Mann-Whitney test by ranking individual patients in the two groups with respect to the number of arrhythmia events or the no. of hours which arrhythmia were observed.

The study evaluated the efficacy of intravenous mexiletine in 10 patients with symptomatic sustained recurrent ventricular tachycardia (VT). Mexiletine was administered intravenously at a dose of 3 mg/kg over 5 minutes, or until VT resolved if it occurred before the full dose. Three patients (1, 3, and 6) experienced recurrent sustained VT on the first day while receiving oral mexiletine 200 mg every 8 hours. In these cases, intravenous mexiletine at 30-50 mg doses, in addition to oral therapy, immediately suppressed the VT episodes. For these three patients, increasing the oral mexiletine dose from 200 mg to 400 mg every 8 hours prevented further VT recurrences. The findings indicated that the initial arrhythmia control was inadequate due to subtherapeutic plasma mexiletine concentrations. The majority of patients experienced non-cardiac toxicities like nausea, vomiting, confusion, and tremor after intravenous mexiletine administration. Notably, in patients 1, 3, and 6, the small intravenous mexiletine doses (30-50 mg) promptly suppressed further VT episodes during oral therapy, suggesting the initial oral dose was suboptimal. By increasing the oral mexiletine dose to 400 mg every 8 hours, no patient experienced VT recurrence during the 3-month follow-up period. The study concluded that mexiletine may be effective in suppressing sustained VT related to chronic ischemic heart disease. The findings highlight the importance of achieving therapeutic plasma concentrations, either through intravenous loading or optimized oral dosing, for adequate arrhythmia control with mexiletine.

The study examined mexiletine's efficacy and tolerability in patients with refractory ventricular arrhythmias and ischemic heart disease, who were not responsive to standard antiarrhythmic treatments. Mexiletine was initiated at 600 mg/day, with some patients requiring a dose reduction due to mild intolerance. Primary outcomes included the total number of ventricular tachycardia (VT) and ventricular fibrillation (VF) episodes post-treatment initiation, while secondary outcomes involved implantable cardioverter-defibrillator (ICD) interventions and mexiletine discontinuation rates. The study enrolled 34 consecutive patients, predominantly

male, with a mean age of 74.0 years. After mexiletine initiation, there was a significant reduction in VT/VF episodes and ICD interventions compared to the pre-treatment period. However, 13.9% of patients discontinued mexiletine due to severe side effects. The findings suggest that mexiletine treatment led to a notable decrease in ventricular arrhythmias in patients with ischemic heart disease who were unresponsive to conventional therapies [REDACTED]

Mexiletine was evaluated in a study involving 28 subjects with recurrent ventricular tachycardia, ventricular fibrillation (22 subjects), or symptomatic complex ventricular ectopy (6 subjects). These subjects had arrhythmias that were either resistant to other antiarrhythmic drugs or could not tolerate conventional therapy. Mexiletine was administered at maximum daily doses ranging from 600 to 1,200 mg, based on the subject's clinical condition. The response to mexiletine was assessed through continuous ECG monitoring, and in five cases, programmed electrical stimulation was used. The results showed that mexiletine abolished the arrhythmia in 12 cases, but four of these subjects could not tolerate long-term therapy. In 10 subjects, mexiletine was ineffective in controlling the arrhythmia. Seven subjects experienced significant adverse reactions during short-term mexiletine dosing, leading to discontinuation of the drug in six subjects after the first few doses, preventing evaluation of its efficacy. The study concluded that while mexiletine demonstrated antiarrhythmic efficacy in some patients with life-threatening ventricular arrhythmias refractory to conventional drugs, its use was significantly limited by adverse effects. The findings highlight the need for careful patient selection and monitoring when considering mexiletine therapy for refractory ventricular arrhythmias [REDACTED]

Two cases of life-threatening ventricular arrhythmia (torsade de pointes) due to chronic mild hypokalaemia, caused by hyperaldosteronism and familial periodic paralysis were treated by correction of the hypokalaemia, supplemented by mexiletine (100 mg 6-hourly in one case and 200 mg 6-hourly in another case), controlled the arrhythmias [REDACTED]

A double-blind, crossover study evaluated mexiletine's efficacy in reducing premature ventricular complexes (PVCs) compared to a placebo in 12 patients with a median of 294 PVCs per hour. Eleven patients completed the 4-week trial, receiving both mexiletine and placebo treatments in a crossover design. Ambulatory electrocardiographic (Holter) recordings were obtained at the end of each treatment period. Mexiletine significantly reduced PVC frequency by 66%, compared to a 3% reduction with placebo ($p = 0.032$). It also effectively decreased the median number of ventricular couplets observed per hour. Patients received mexiletine dosages ranging from 100 mg to 400 mg every 8 hours. Importantly, mexiletine did not cause significant changes in baseline values, including electrocardiographic intervals, blood pressure, or heart rate, indicating a favorable safety profile. In summary, this study demonstrated mexiletine's efficacy in reducing PVCs and ventricular couplets compared to placebo, with tolerable safety at studied dosages [REDACTED]

A double-blind, crossover study evaluated mexiletine's efficacy and optimal dose for reducing premature ventricular complexes (PVCs) in 26 ambulatory patients with an average of 427.9 PVCs/hour. The primary goal was to identify the dose that could reduce PVC frequency by $\geq 50\%$. After a 3-week treatment period, 24 patients completed the trial. Mexiletine significantly reduced PVCs by 63.8% compared to a 7.5% increase with placebo. In 19 responders ($\geq 50\%$ PVC reduction), the effective dose was 600 mg/day (200 mg every 8 hours).

Notably, non-responders had therapeutic mexiletine plasma levels similar to responders. The study demonstrated mexiletine's efficacy in managing ventricular arrhythmias, with the 600 mg/day dose achieving substantial PVC reduction and minimal side effects in most patients

The study examined oral mexiletine's impact on left ventricular function and arrhythmias in 29 patients with chronic ventricular premature complexes (VPCs) and moderately reduced to normal ejection fraction (EF). Patients received incremental doses over 3 months: 600 mg, 900 mg, and 1,200 mg daily. VPC rate reduction was significant, especially in patients with baseline $EF \leq 40\%$. Ventricular tachycardia episodes were suppressed in nearly all patients, with minimal proarrhythmic effects. Resting or exercise EF remained stable, and no correlation was found between changes in arrhythmia frequency and EF. No congestive heart failure symptoms were reported, suggesting long-term mexiletine use is safe, even in patients with reduced LV function

In a study involving 9 patients with recurrent and refractory ventricular tachycardia, a treatment protocol combining mexiletine and amiodarone was evaluated. Initially, both drugs were administered intravenously for the first two days, followed by oral administration from day three onwards. The dosages were 1,000 mg/day for mexiletine and 1,500 mg/day for amiodarone intravenously, with subsequent oral doses of 600 mg/day for both drugs. The first three critically ill patients with a high burden of ventricular tachycardia episodes showed a remarkable response, with complete suppression of tachycardia within three days. In the remaining six cases, programmed electrical stimulation on day seven revealed no inducible arrhythmia. During a 6-month follow-up, two patients succumbed to heart failure, one died suddenly post-discharge, and another died after aneurysmectomy and recurrence. The majority of patients remained asymptomatic. The study demonstrated the synergistic effect of combining a class I antiarrhythmic agent (mexiletine) with a class III agent (amiodarone) in managing refractory ventricular arrhythmias, showing promising results in suppressing recurrent and drug-resistant ventricular tachycardia episodes

In 44 patients with drug-resistant ventricular tachyarrhythmias, mexiletine's efficacy was evaluated, including programmed ventricular stimulation in 33 patients. Mexiletine did not alter ventricular refractory period, QTc, or tachyarrhythmia induction/termination methods. In 21 patients, mexiletine alone increased mean VT cycle length from 270 ± 49 to 313 ± 80 ms ($p < 0.002$). Overall, VT remained inducible in 25 patients on mexiletine alone/combined therapy. VT induction was prevented in 8 patients (3 on mexiletine alone). Mexiletine alone/combined suppressed clinical VT recurrence in 5/11 patients without electrophysiology study. 13 patients were discharged on mexiletine regimens and remained arrhythmia-free for 7.7 ± 4.1 months on average, suggesting potential utility in drug-resistant VT

A study examined the efficacy of mexiletine, alone or with class IA agents, in 35 patients with recurrent sustained ventricular tachycardia (VT) or ventricular fibrillation unresponsive to standard antiarrhythmic drugs. While mexiletine alone effectively treated VT in a minority of patients, combining it with class IA agents significantly reduced ventricular ectopy and improved long-term arrhythmia-free survival, regardless of initial test outcomes. Among the patients discharged on mexiletine regimens, with some also receiving class IA agents, those with an ineffective regimen by initial testing experienced a marked reduction in ventricular

ectopic activity, with favorable outcomes during an 18±13 month follow-up. Overall, combining mexiletine with class IA agents showed promising results in managing refractory VT or ventricular fibrillation, suggesting a potential therapeutic strategy for such challenging cases [REDACTED]

A double-blind, parallel-group trial involving 491 patients with ventricular arrhythmias compared the antiarrhythmic efficacy of oral mexiletine and quinidine at 29 clinical centers. After 12 weeks of therapy, 31% of patients in the mexiletine group and 32% in the quinidine group responded, with similar proportions of responders across diagnostic categories. Concomitant use of digitalis, diuretics, or β -blockers did not significantly affect response rates, except for a higher response rate (43%) with mexiletine plus β -blockers compared to mexiletine alone (26%). No statistically significant differences were observed in the magnitude of ventricular premature complex, couplet, or tachycardia rate reductions between the two groups. The majority of responders required only the smallest single dose. The study demonstrated mexiletine as an alternative to quinidine for treating ventricular arrhythmias, with comparable efficacy and tolerability profiles [REDACTED]

The study evaluated the effectiveness of oral mexiletine and disopyramide in treating recurrent sustained ventricular tachycardia (VT), a serious arrhythmia. Thirty-four patients with a history of recurrent VT, mostly due to coronary heart disease or cardiomyopathy, received mexiletine (400 mg loading dose followed by 600-1000 mg daily) or disopyramide (450-900 mg daily) for at least four days. Their response was assessed using programmed ventricular stimulation, which induces VT under controlled conditions. Complete suppression of VT was achieved in only a small portion of patients: 3 out of 30 with mexiletine (10%) and 1 out of 25 with disopyramide (4%). While disopyramide slowed induced VT rates significantly, mexiletine did not. Over a 24-month follow-up, 19 patients continued drug therapy. Complete VT suppression during PVS predicted long-term freedom from VT recurrence. However, for patients not achieving complete suppression, both drugs reduced VT frequency and rate, albeit partially. Despite this, 31% of this subgroup experienced mortality during the study. The study concluded that while mexiletine and disopyramide could completely suppress VT in a minority of previously drug-resistant patients, overall efficacy remained limited [REDACTED]

Mexiletine was utilized in 21 patients with refractory ventricular arrhythmias, primarily due to ischemic heart disease. Among them, only three achieved arrhythmia control without side effects as the dosage was increased. Seventeen patients experienced partial response, with ventricular ectopic depolarizations (VEDs) suppression averaging 62.5% with mexiletine alone. However, side effects limited therapy at an average dose of 950 mg/day. Quinidine, previously ineffective or intolerable, was combined with well-tolerated mexiletine doses in 17 patients, resulting in significantly improved antiarrhythmic response (mean VEDs suppression: 85.9%). Only one patient continued to experience ventricular tachycardia, with side effects occurring in only 12% of cases. Upon discontinuation of mexiletine, complex ventricular arrhythmias recurred in nine patients, indicating the necessity of combination therapy. ECG intervals were monitored throughout treatment, revealing prolongation of the coupling interval with mexiletine, further extended with quinidine, and subsequent QTc interval prolongation upon mexiletine withdrawal. This suggests that mexiletine attenuated the quinidine-induced QTc interval increase. Over 18 months of follow-up, three deaths occurred, one due to heart failure and two related to noncompliance with treatment. Combining quinidine, known for prolonging repolarization, with mexiletine, which shortens action potential duration, led to

enhanced antiarrhythmic efficacy, highlighting the potential of drug combinations with differing electrophysiological properties for improved treatment outcomes [REDACTED]

Mexiletine's efficacy was assessed in 59 patients with acute or chronic ventricular arrhythmias. Treatment success, defined as arrhythmia abolition or >95% reduction in extrasystole frequency, was observed in 43 patients (72%), with partial success in 12 (20%). Only 4 patients (7%) showed no response to the therapy. Notably, 83% of patients treated intravenously initially responded to mexiletine. Partial success correlated with inadequate dosing. Among patients treated orally post-myocardial infarction, all six had adequate control of ventricular arrhythmias. Additionally, six out of ten patients receiving oral mexiletine for up to 14 months had successful treatment. Mexiletine demonstrated efficacy either alone or in combination with other drugs. The study identified mexiletine as a promising therapeutic option for managing various ventricular arrhythmias. Its high success rate in abolishing or reducing arrhythmias showcases its potential clinical utility. Furthermore, the positive response observed in patients previously unresponsive to other medications, including intravenous lignocaine and procainamide, highlights mexiletine's effectiveness in challenging cases. Moreover, the study noted that adequate dosing was crucial for achieving optimal outcomes with mexiletine. In cases where treatment was classified as partly successful, it was found that insufficient doses were administered. This underscores the importance of carefully titrating the dosage to ensure adequate control of ventricular arrhythmias. Overall, the findings underscore mexiletine's role as an effective treatment option for both acute and chronic ventricular arrhythmias, offering hope for patients with arrhythmias refractory to other medications [REDACTED]

The research investigated mexiletine's effectiveness and tolerability in 41 patients experiencing ventricular arrhythmias unresponsive to standard therapies. Mexiletine was administered initially with a loading dose of 400 mg, followed by maintenance doses ranging from 400-1,200 mg/day, divided as necessary, titrated upwards until achieving a satisfactory response, reaching a maximum dose of 1,200 mg/day, or encountering dose-related toxicity. Among patients with electrically inducible ventricular arrhythmias, mexiletine completely suppressed arrhythmias in 13 out of 35 patients and improved responses in 7 out of 12 patients with partial suppression. In cases of recurrent spontaneous ventricular tachycardia not inducible by stimulation, mexiletine effectively controlled arrhythmia in 4 out of 6 patients. Crucially, complete acute arrhythmia suppression with mexiletine predicted long-term freedom from recurrence in 16 out of 17 patients during a mean 12.6-month follow-up. The study findings underscore mexiletine's well-tolerated and efficacious prophylaxis against recurrent ventricular arrhythmias in a notable proportion of patients resistant to conventional drug therapies [REDACTED]

The study assessed the efficacy of mexiletine in treating recurrent ventricular tachycardia and predicting long-term arrhythmia suppression based on acute and short-term response. Patients experiencing frequent episodes ($\geq$ three per 24 hours) of ventricular tachycardia ($\geq$ three consecutive ventricular ectopic beats) received intravenous mexiletine with a 200 mg dose over 5 minutes immediately following an episode, with an additional 200 mg dose over 1 hour if recurrence occurred within 15 minutes. Oral mexiletine, 200 mg every 8 hours, was initiated if no recurrence was observed after approximately 2 to 3 hours. Five patients with frequent ventricular tachycardia responded to intravenous mexiletine. Intravenous mexiletine prevented ventricular tachycardia induction in only one patient during programmed ventricular

stimulation. Upon short-term oral therapy, seven out of eight patients experienced a >83% reduction in total ventricular ectopic beats. Of the seven patients on long-term oral therapy, one experienced recurrent ventricular tachycardia on day 5 and discontinued the drug, while another developed severe persistent vomiting on day 4 and terminated mexiletine therapy. The remaining five patients remained symptom-free during a mean follow-up of 15 months (range 4 to 22 months), all initially responding to mexiletine. The study suggests that acute and short-term ventricular tachycardia suppression by mexiletine could predict long-term efficacy [REDACTED]

The study evaluated the effect of oral mexiletine therapy on ventricular arrhythmias in 58 patients who had not responded to conventional antiarrhythmic drugs. Patients received a mean daily mexiletine dose of 652 mg (range 250-1,500 mg) for a mean duration of 14.4 months. Mexiletine was associated with a 52% decrease in total premature ventricular complexes over 24 hours compared to control. 19 patients (36.5%) experienced greater than 83% reduction in ventricular ectopic rhythm. However, the drug was discontinued in 6 of these 19 patients due to side effects in 5 patients after a mean of 29.6 weeks, and 1 patient died suddenly, indicating effective arrhythmia suppression without significant side effects in only 13 (25%) patients during long-term therapy. Adjusting dosage to achieve therapeutic blood levels provided similar efficacy as the maximum tolerated dose. Mexiletine reduced episodes of ventricular tachycardia by 48%, and 5 of 10 patients with prior cardiac arrest remained free of symptomatic ventricular tachyarrhythmias for 14.8 months on average [REDACTED].

The antiarrhythmic efficacy of mexiletine hydrochloride (Mexitil) was evaluated in 100 patients with potentially lethal and drug-resistant ventricular arrhythmia. The efficacy of arrhythmia suppression was assessed by Holter monitoring. The overall arrhythmia suppression of ventricular premature contractions of 70% and greater was low and seen in only 22% of patients, with an additional 16% responding to a combination of mexiletine and an additional antiarrhythmic drug. The suppression of high-grade forms, couplets of 90% and greater, and complete abolition of nonsustained runs of ventricular tachycardia was achieved in 22% of patients, with 9% responding to the addition of another antiarrhythmic agent. Ventricular premature contractions, couplets, and nonsustained ventricular tachycardia were suppressed in only 16% of the cohort [REDACTED]

The efficacy of mexiletine in patients with recurrent ventricular tachyarrhythmias and/or electrical storm events, unresponsive to standard treatments, was assessed in a retrospective cohort analysis. Between January 2011 and September 2015, 17 patients were treated with mexiletine at the institution. Primary endpoints included the total number of electrical storm events and ventricular tachycardia/ventricular fibrillation (VT/VF) episodes post-mexiletine therapy, with secondary endpoints being the total number of implantable cardioverter-defibrillator (ICD) therapies and therapy discontinuation. Patients served as self-controls. The mean age of the 11 male patients was 64.2 ± 15.4 years, with a median mexiletine treatment duration of eight months (interquartile range [IR]: 1-22 months). Mexiletine dosages were 600 mg/day in 13 patients and 400 mg/day in four, with adjustments made in four patients during treatment (range: 400 to 600 mg/day). Mexiletine treatment significantly reduced electrical storm events (14 vs. two episodes; median and IR for 17 patients: 1 [0-1] vs. 0 [0-0], $p = 0.0010$), VT/VF episodes (285 vs. 74 episodes; median and IR for 17 patients: 7 [5-27] vs. 0 [0-5], $p = 0.0115$), and ICD interventions (317 vs. nine interventions; median and IR for 17

patients: 10 [5-25] vs. 0 [0-2], $p = 0.0006$), compared to the period before treatment initiation. Mexiletine demonstrated sufficient tolerability as an antiarrhythmic drug in short-term treatment for ventricular tachyarrhythmias in this population, suggesting potential efficacy in managing recurring ventricular tachyarrhythmias or electrical storm events [REDACTED]

The study investigated the effectiveness of intravenous mexiletine in controlling repetitive ventricular ectopy and ventricular tachycardia, and explored the transition to oral mexiletine therapy. Fifteen patients, 13 with ventricular tachycardia and all with recurrent ventricular ectopy, were included. Intravenous mexiletine was administered at 10 mg/min for 30 to 60 minutes. Results showed effective suppression of ventricular ectopy in 10 patients (66.7%) with minimal side effects. Following intravenous treatment, 10 patients initiated oral mexiletine therapy at 10 mg/kg/24 hr, maintaining arrhythmia suppression in 8 patients. However, 3 of these patients experienced side effects, managed by dose reduction in one case. For 2 patients not responding to the initial oral dose, a higher dose (15 mg/kg/24 hr) was effective in one patient. The study concluded that intravenous mexiletine rapidly controls non-sustained repetitive ventricular arrhythmias in about two-thirds of patients. Transition to oral therapy is feasible in many cases, though dose adjustments may be needed to balance efficacy and tolerability. The findings suggest intravenous mexiletine as a prompt treatment for ventricular arrhythmias, with potential for oral maintenance therapy, but emphasize careful monitoring and dose management during the transition [REDACTED]

The effectiveness of mexiletine, both alone and in combination with a class IA antiarrhythmic drug, was assessed in 159 patients with drug-resistant ventricular tachycardia (VT) through a series of electrophysiologic studies and a five-year clinical follow-up. Mexiletine alone suppressed electrically-inducible VT in 23% of patients, while the combination therapy was effective in 29% of cases. Mexiletine showed significantly higher efficacy in patients with non-sustained VT or ventricular fibrillation compared to those with sustained VT ($p < 0.005$). After one and four years of treatment, 18% and 42% of patients on mexiletine alone had died suddenly or experienced recurrent symptomatic VT, respectively, versus 11% and 25% of those on the combined regimen; however, this difference was not statistically significant. Although mexiletine often caused reversible adverse reactions, it had to be discontinued permanently in 9% (8/92) of patients due to intolerable side effects. Thus, while mexiletine effectively suppressed VT in a subset of drug-refractory patients, both alone and in combination with a class IA agent, the combined regimen tended to yield better long-term outcomes, despite a significant incidence of adverse reactions leading to treatment discontinuation in some cases [REDACTED]

Dosage and administration

(SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021)

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.

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.

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.

Conclusion:

To summarize, the effectiveness of Mexiletine was found to be good in above mentioned proposed indication. Above provided summary and information extracted from peer reviewed journals and other sources confirms that use of Mexiletine in the proposed indication is efficacious.

2.5.5 Overview of Safety

The European Summary of Product Characteristics and USA prescribing information/labels of approved and registered product of Mexiletine hydrochloride confirmed by respective medical authority's mirrors the results from clinical studies as well as the experience from clinical use in practice. Therefore, the discussion in the following section is based on the information given in published literatures, approved packages as well as data reported in post-marketing experience of approved formulation of Mexiletine hydrochloride 100 mg hard capsules.

Adverse effects have been ranked under headings of frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$; $< 1/10$); uncommon ($\geq 1/1,000$; $< 1/100$); rare ($\geq 1/10,000$; $< 1/1,000$); very rare ($< 1/10,000$); frequency not known (cannot be estimated from the available data) (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

Table 15: Adverse effects

System Organ Class	Very Common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ 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		vertigo, tinnitus				

Mexiletine hydrochloride 100 mg and 200 mg hard capsules

disorders						
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			

Scientific literatures supporting the adverse events of Mexiletine

In a study, 24 patients with ventricular arrhythmias were treated with oral mexiletine for 1 to 16 months (total 10.4 patient-years). The usual starting dose was 400-600 mg, followed by 150-350 mg every 8 hours for maintenance. Toxic symptoms were observed in 8 patients, severe enough to permanently stop therapy in 3 and require dose reduction in 4 others. The most common toxic effects were fine hand tremor, dizziness, blurred vision, and nausea, with frail elderly females being most susceptible. The mean toxic concentration range was 1.5-3.0 µg/mL, with an approximate mean of 2 µg/mL. Regular blood tests showed no abnormalities, and antinuclear factor (ANF) tests remained negative [REDACTED]

The study evaluated the long-term safety and tolerability of mexiletine in 12 patients who received the drug for various durations. Mexiletine was given to these patients for different periods of time varying from 4 to 96 months, with a mean of 47.8 months. At the latest follow-up in August 1983, five patients had been taking mexiletine for an extended period, ranging from 74 to 96 months, with a mean duration of 85 months. During the study, mexiletine was well-tolerated, and no serious side effects were observed in these patients receiving long-term treatment. Importantly, there was no rise in antinuclear factor titer, suggesting no increased risk of autoimmune reactions with prolonged mexiletine use. Additionally, the serum level of mexiletine was easily maintained within the therapeutic range, and most side effects correlated closely with the drug level, allowing for effective management of adverse effects. Based on these findings, the study concluded that mexiletine can be administered for a long time as a safe alternative to other antiarrhythmic drugs. The absence of serious side effects, lack of autoimmune reactions, and the ability to maintain therapeutic levels while managing side effects supported the long-term use of mexiletine in clinical practice [REDACTED]

A double-blind, crossover study evaluated the safety of mexiletine in reducing premature ventricular complexes (PVCs) compared to placebo. Twelve patients with a median of 294 PVCs/hour participated, and 11 completed the 4-week trial. Mexiletine significantly reduced PVCs by 66% versus 3% with placebo ($p=0.032$) and decreased ventricular couplets. After 4 weeks, patients tolerated doses ranging from 100 to 400 mg every 8 hours without significant adverse effects on electrocardiographic intervals, blood pressure, or heart rate. Minor gastrointestinal and neurological symptoms were reported but did not require dose adjustments. The study demonstrated mexiletine's favorable safety profile in managing ventricular arrhythmias [REDACTED]

A double-blind, parallel-group trial involving 491 patients with ventricular arrhythmias compared the safety of oral mexiletine and quinidine at 29 clinical centers. Side effects led to study withdrawal in 40% of mexiletine patients and 33% of quinidine patients, mostly within the first 12 weeks. Side effects accounted for more treatment failures than lack of arrhythmia suppression. The most common adverse events involved the gastrointestinal and central nervous systems. Diarrhoea was more frequent with quinidine, while upper gastrointestinal distress and CNS disturbances occurred more often with mexiletine. Serious adverse events like syncope, myocardial infarction, heart failure, and cardiogenic shock were rare and not considered drug-related. No significant changes in laboratory parameters, heart rate, or blood pressure were noted. The study highlighted the comparable safety profiles of mexiletine and

quinidine, with side effects being the primary reason for treatment discontinuation in both groups [REDACTED]

A study assessed mexiletine's safety in preventing arrhythmias among acute myocardial infarction patients. Ninety-nine patients were randomly assigned to receive either mexiletine or a placebo. The treatment began with an initial intravenous dose of 250 mg, followed by oral doses. However, two patients experienced hypotension and bradycardia following mexiletine infusion, with detectable serum concentrations. Additionally, one patient developed conduction disturbances necessitating temporary pacing, while another experienced a short episode of III degree AV-block. Various side effects were observed, including hypotension, bradycardia, pulmonary edema, and vomiting. Notably, two patients exhibited probable neurological side effects: one reported numbness all over the skin, and another felt unusually sleepy. In total, two patients discontinued the study due to suspected side effects. During the first hour, hypotension, bradycardia, or both occurred in five mexiletine patients and two placebo patients in the acute myocardial infarction group. Later in the study, hypotension and bradycardia were found in four mexiletine patients and eleven placebo patients. Pulmonary edema occurred in two mexiletine patients and one placebo patient. Overall, vomiting was more frequent in the mexiletine group on the first day, although not statistically significant [REDACTED]

The safety of mexiletine was assessed in patients with recurrent ventricular tachyarrhythmias and/or electrical storm events, where standard treatments had failed. A retrospective cohort analysis revealed that mexiletine was well-tolerated, with no notable side effects observed in 10 patients (58.8%). Mild temporary side effects occurred in four patients (23.5%), including temporary and mild abdominal pain in two patients, extremities tremor in one patient, and dizziness in one patient, which did not necessitate treatment discontinuation. Overall, sufficient tolerability of mexiletine was observed in 14 out of 17 patients (82.4%). Severe side effects requiring treatment discontinuation occurred in three patients (17.6%), including severe abdominal pain in two patients and severe dizziness in one patient. All side effects occurred within several days after initiating therapy. Notably, no deaths were observed during mexiletine therapy [REDACTED]

Special warnings and precautions for use

(SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

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

High mexiletine plasma levels may be observed in patients with CYP2D6 poor metabolism or in patients who take medicinal products that inhibit CYP2D6. 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.

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.

A study examined LV contractility in 8 patients with congestive heart failure and significant mitral regurgitation before and after 2 to 4 weeks of mexiletine (300 mg) administration. LV contractility was measured using Doppler echocardiography. Despite the treatment, there were no significant changes observed in LV contractility, left ventricular ejection fraction, or left ventricular and left atrial dimensions. This suggests that mexiletine does not affect LV contractility in these patients [REDACTED]

In a case report, a 53-year-old man with heart failure and ischemic heart disease experienced a sudden drop in platelet counts to $140000/\text{mm}^3$ four days after starting mexiletine treatment (600 mg/d). Thrombocytopenia persisted despite discontinuing mexiletine but resolved within 10 days. Other clotting tests remained normal. Platelet examination showed increased size, and antibody testing showed no abnormalities [REDACTED]

Neutropenia appeared in nine patients during an open-label emergency use program in the US where they received mexiletine (MXL), alongside other medications, making it challenging to pinpoint MXL's role. Using BARDI to analyze these cases, in potential causes, BARDI enabled to assess MXL's contribution, revealing a minimal risk of MXL-induced neutropenia—roughly 1 case per 11,741 patients, or less than 1 per 10,000. This risk is notably lower than that associated with other antiarrhythmic drugs like procainamide (0.55%) [REDACTED]

An 82-year-old man developed fever, cough, and a rash while taking mexiletine for heart issues. Tests revealed eosinophilia, liver enzyme elevation, and lung nodules. Biopsies confirmed eosinophilic infiltration. Suspecting mexiletine, it was stopped and prednisolone started, leading to improvement. A patch test confirmed mexiletine as the cause. This case highlights drug-induced hypersensitivity syndrome, especially in older Japanese males taking mexiletine [REDACTED]

In another case report, a 70-year-old woman, previously on mexiletine hydrochloride for four weeks, presented with systemic oedematous erythema and subacute progressive gait disturbance. Evaluation revealed lymphadenopathy with atypical lymphocytosis and eosinophilia, alongside human herpesvirus 6 (HHV-6) reactivation. Neurological examination showed nearly complete loss of joint positional sense, absent tendon reflex, marked pseudoathetosis, and positive Romberg's sign. Skin biopsy demonstrated spongiosis with lymphocyte infiltration, leading to a diagnosis of acute sensory ganglionopathy secondary to Drug-Induced Hypersensitivity Syndrome (DIHS). Methylprednisolone alleviated DIHS-induced symptoms but only partially improved sensory ganglionopathy, despite subsequent intravenous immunoglobulin therapy. This case raises the possibility of HHV-6 reactivation contributing to sensory ganglionopathy in DIHS [REDACTED]

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. As a precautionary measure, it is preferable to avoid the use of mexiletine during pregnancy (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

A 26-year-old woman with mitral valve prolapse and ventricular tachycardia was treated with mexiletine and atenolol throughout pregnancy and after delivery. Her arrhythmia remained stable during pregnancy without reported adverse effects from mexiletine. Two urinary tract infections occurred during pregnancy, and concerns arose about possible intrauterine growth retardation, though not confirmed by ultrasound. Mexiletine, being lipid soluble, crosses the placenta and is excreted in breast milk. The report advises caution with mexiletine use during pregnancy and breastfeeding, suggesting considering alternatives to breastfeeding while the mother is on mexiletine [REDACTED]

Lactation

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

The study evaluated the transfer of mexiletine from maternal plasma to breast milk in a 30-year old woman taking mexiletine (200 mg) and propranolol every 8 hours after delivery. Twelve paired breast milk and blood samples were collected between 2-5 days postpartum. Mexiletine was measurable in all breast milk and plasma samples. Importantly, the milk-to-plasma ratio for mexiletine ranged from 0.79 to 1.89, with a mean of 1.45. This indicates that mexiletine concentrations in breast milk were comparable to or slightly higher than maternal plasma levels. The study highlights that mexiletine readily crosses into breast milk, potentially exposing breastfed infants to significant levels of the drug [REDACTED]

Contraindication:

(SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021)

- 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.

A 45-year-old Japanese man developed a rash, fever, hepatitis, and lymphadenopathy, diagnosed as Drug-Induced Hypersensitivity Syndrome (DIHS) from mexiletine hydrochloride. Treatment with steroids was initiated. Serological and PCR testing revealed elevated HHV-6 and -7 antibodies and HHV-7 DNA in samples, suggesting HHV-7 reactivation as a possible cause of the syndrome [REDACTED]

In a case study, a 64-year-old man developed a severe rash, fever, eosinophilia, and liver dysfunction 30 days after taking mexiletine for postherpetic neuralgia. While intravenous dexamethasone relieved his fever, the rash persisted for four weeks. Patch testing confirmed mexiletine hypersensitivity syndrome, indicating a serious adverse skin reaction [REDACTED]

In another case, a 54-year-old man with dilated cardiomyopathy developed Drug-Induced Hypersensitivity Syndrome (DIHS) from mexiletine, prescribed for ventricular tachycardia. Prednisolone initially improved his symptoms, but nine days later, the patient experienced systemic deterioration and cardiogenic shock. Despite normal coronary arteries, the patient needed percutaneous cardiopulmonary support due to worsening heart function. Biopsy confirmed fulminant myocarditis. This case underscores the risk of severe reactions, including myocarditis, from cardiac medications like mexiletine [REDACTED]

Intravenous mexiletine, given at doses of 200 to 250 mg over 5 minutes followed by continuous infusion of 60 to 90 mg per hour, was studied in 25 patients. Most had plasma levels above the therapeutic limit. Mexiletine had limited impact on sinus frequency and atrial refractoriness but increased AV nodal conduction time by 11 ms on average and shifted the Wenckebach point to a lower atrial rate. It inconsistently influenced AV node refractory periods but notably increased the functional refractory period in 12 out of 14 patients. HV intervals increased by 11 ms in 8 patients and remained unchanged in 17. Non-cardiac side effects occurred in 7 patients, and cardiac side effects, including one serious event, in 2. These findings suggest that mexiletine shares properties with procainamide and quinidine, particularly in patients with conduction defects. Caution is warranted in patients with pre-existing conduction impairments [REDACTED]

The impact of an intravenous dose of mexiletine (2 mg/kg body wt of mexiletine over a period of 10 min) on the electrophysiological characteristics of the intact human heart was examined

in ten individuals without cardiovascular disease. Mexiletine did not induce noteworthy alterations in the sinus node recovery time, corrected sinus node recovery time, or in the effective refractory periods of the atria, atrioventricular node, and ventricles. Additionally, mexiletine did not significantly affect proximal atrioventricular conduction. However, the drug did prolong atrioventricular conduction distal to the bundle of His in all ten subjects by an average of 6 milliseconds, a change that was statistically significant ($P < 0.01$). Caution is advised when administering the drug to patients with conduction disturbances [REDACTED]

Cardiodepressant effects of mexiletine in patients with severe left ventricular dysfunction was assessed. In a study involving 20 patients with severe chronic heart failure, the hemodynamic response to an oral loading dose of mexiletine (400 mg) was evaluated. Mexiletine led to significant hemodynamic decline, with a decrease in stroke work index observed in 18 patients. Two hours post-mexiletine administration, mean cardiac and stroke work indexes decreased by 15% and 25%, respectively (both $p < 0.001$), while heart rate and systemic vascular resistance increased by 10% and 20%, respectively (both $p < 0.05$). Additionally, left ventricular filling pressure and right atrial pressure increased by 37% and 36%, respectively (both $p < 0.001$), without any change in mean arterial pressure. Five patients experienced clinical deterioration, with onset of resting dyspnea coinciding with peak hemodynamic effects. Plasma mexiletine concentrations were within the therapeutic range (0.5 to 2.0 micrograms/ml) in most patients, but the level significantly influenced the hemodynamic response. Specifically, patients with higher plasma concentrations (above the median of 1.3 micrograms/ml) experienced a 38% decrease in stroke work index, compared to 13% in those with lower concentrations. In summary, while mexiletine may induce cardiodepressant effects in severe left ventricular dysfunction patients, dosing resulting in higher plasma levels, albeit still within therapeutic range, is more likely to precipitate hemodynamic deterioration [REDACTED]

In a study of 20 patients with significant left ventricular dysfunction, the effects of quinidine and mexiletine were compared. Quinidine led to vasodilation, lowering blood pressure and vascular resistance, while mexiletine increased vascular resistance and raised blood pressure. Mexiletine also decreased cardiac performance, unlike quinidine. These differences were significant across all parameters measured. Clinical effects included increased dyspnea with mexiletine and hypotension with quinidine in some patients. Drug concentrations were within therapeutic ranges. This study highlights the importance of evaluating medication effects in heart failure patients to better understand potential adverse consequences in this high-risk population [REDACTED]

A study evaluated the effects of disopyramide and mexiletine, both individually and in combination, on chronic ventricular arrhythmias in 29 patients. In single-drug therapy, patients received 100 mg of disopyramide or 150 mg of mexiletine orally every 8 hours, three times daily. In combination therapy, doses were reduced to 50 mg of disopyramide and 100 mg of mexiletine every 8 hours, three times daily. Compared to baseline, there were no significant differences in PQ or QRS intervals during any therapy. However, the QTc interval was significantly prolonged with disopyramide alone compared to combination therapy ($P < 0.05$). Additionally, PI was significantly reduced and VI tended to increase with disopyramide therapy alone compared to combination therapy [REDACTED]

Overdose and its management

(SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021)

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

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 (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021).

A case involving a fatal overdose of mexiletine was presented. Toxicological analysis revealed the following tissue distribution of mexiletine: heart blood, 44.8 micrograms/mL; femoral blood, 10.0 micrograms/mL; vitreous, 8.6 micrograms/mL; liver, 171.6 micrograms/g; brain, 84.0 micrograms/g; and gastric contents, 1464 mg [REDACTED].

Conclusion

From the above cited references and information, it can be concluded that Mexiletine has been found to be well tolerated with good safety margin. The side effects observed in clinical trials are transient in nature and are not significantly different from the placebo group. The side effects were categorized as rare and uncommon indicates that with appropriate clinical management these adverse effects can be avoided and can be reversed, if there is any incidence.

In addition to available information, post marketing data available from various resources also suggests that there is no any safety signal observed so far with Mexiletine in clinical settings. Mexiletine has adverse effects similar to other drugs however by following the proper and optimal clinical approach and by careful monitoring, these effects can be minimized/avoided. Conclusively, Mexiletine hydrochloride 100/200 mg hard capsules is safe in all appropriate proposed indications with recommended/prescribed posology.

2.5.6 Benefits and Risks Conclusions

Mexiletine oral dosage form has been used since long time in clinical practice. Being one of the most used standard oral formulation, its efficacy and safety has been proven by the worldwide clinical experience. Based on comprehensive literature data, the benefit/risk balance of the Mexiletine hard capsules is favourable, No additional toxicological or clinical studies were deemed necessary for this application.

The literature research strategy outlines the indications, pharmacology, efficacy, methods of administration, important adverse effects and contraindications of Mexiletine.

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.

Mexiletine typically does not alter conduction velocity but may slow conduction in patients with pre-existing conduction abnormalities. In those with sick sinus syndrome, it can significantly depress the sinus rate and prolong sinus node recovery time. Mexiletine does not significantly affect resting membrane potential, sinus node automaticity, left ventricular function, systolic arterial blood pressure, AV conduction velocity, QRS, or QT intervals. Haemodynamic studies show that oral mexiletine has minor effects on cardiac output, pulmonary capillary wedge pressure, left ventricular end-diastolic pressure, pulmonary diastolic pressure, blood pressure, or heart rate in patients with normal or abnormal myocardial function.

Mexiletine is readily absorbed from the gastrointestinal tract, reaching peak plasma concentrations within 2 to 4 hours after oral administration, with a systemic bioavailability of approximately 90%. The therapeutic range is about 0.5 to 2.0 µg/ml. While food intake does not affect its pharmacokinetics, taking mexiletine after meals is recommended to reduce gastrointestinal side effects. The drug has a large apparent volume of distribution (5 to 10 L/kg), indicating extensive tissue uptake, with protein binding between 55% to 70%. Mexiletine crosses the placental barrier and is present in breast milk. Mexiletine is primarily metabolized in the liver by CYP2D6 enzymes, with involvement of CYP1A2. Its metabolism includes aromatic and aliphatic hydroxylation, dealkylation, deamination, and N-oxidation, followed by conjugation with glucuronic acid. Major metabolites include p-hydroxymexiletine, hydroxy-methylmexiletine, and N-hydroxymexiletine. Poor CYP2D6 metabolizers have lower total and renal clearance, a prolonged elimination half-life, higher exposure, and a lower volume of distribution compared to extensive metabolizers. About 10% of mexiletine is excreted unchanged by the kidneys. The elimination half-life of mexiletine ranges from 5 to 15 hours, with renal excretion accounting for 90% of the dose, including 10% as unchanged drug. Renal clearance varies with urine pH, but this variation is not clinically significant. A linear relationship between dose and plasma concentration is observed in the 50 to 600 mg dose range.

The most common reported adverse events were insomnia, dizziness, tremor, abdominal pain, nausea, vomiting and dyspepsia. The effects are closely related to the plasma concentration of mexiletine and the usually respond to reduction in dosage. Some gastrointestinal disturbances may be due to a direct effect of mexiletine on the gastric mucosa. Overall incidence of adverse effects is high but a large proportion are not serious and can be controlled by dosage reductions or drug administration with food.

Mexiletine can be safely administered in combination with other antiarrhythmic drugs to improve efficacy and tolerability, although its full potential in this regard has yet to be established in clinical trials.

Thus, relative to many other antiarrhythmic drugs, mexiletine can be employed with reduced risk of serious cardiovascular complications in patients with symptomatic ventricular arrhythmias, with or without complicating factors such as congestive heart failure or conduction disturbance (with careful monitoring).

Therapeutic Justification:

Mexiletine hydrochloride 100/200 mg hard capsules is indicated for (SmPC of Mexiletine hydrochloride Hard Capsules, Clinigen Healthcare Ltd. 2021):

- 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.

The therapeutic use of Mexiletine hydrochloride hard capsules in these conditions had been studied by using published literatures; these indications are essentially similar to that promoted from the other brand leaders across Europe. Thus, the use of Mexiletine hydrochloride hard capsules for the proposed indications on the SmPC is therapeutically justified.

Biopharmaceutics

This Marketing Authorization Application (MAA) is submitted as a “bibliographic application”. The scientific literature demonstrated that the active substance in Mexiletine hydrochloride hard capsules has been with well-established medicinal use with acceptable efficacy and safety. The legal basis of the application is that it is bibliographic; therefore, a new bioequivalence study for this application is not required.

Efficacy

There is sufficient available literature that shows that Mexiletine is effective for all the proposed indications. The literature data to support this have been presented in this clinical overview and clinical summary. The product in this application is similar to the existing approved licensed brand product. The active ingredient, dosage form and the route of administration are similar for both products. Thus it is unlikely that any factor related to

bioavailability might adversely affect the efficacy of the product. The studies included in the present document can support the well-known pharmacokinetic, pharmacodynamic and safety profile of Mexiletine.

Dose and Administration

The dosage regimen proposed for Mexiletine hydrochloride hard capsules is similar to that of the authorized brand in the Europe.

Risk/Benefit

This expert report accompanies an application to market Mexiletine hydrochloride 100/200 mg hard capsules.

This medicinal product is to be used in the same way as approved licensed product. The risk/benefit analysis of this formulation is therefore the same as that for the licensed products.

Based on the extensive analysis of literature data, it can be stated that the therapeutic benefit clearly outweighs the possible risk associated with the use of mexiletine as recommended by the applicant.

The medical benefits to be expected from these products are similar to those of existing Mexiletine capsules formulations and as non-proprietary preparation it should offer an additional cost advantage over the existing products. The addition of this formulation to the choice of sources for mexiletine capsule for human use may therefore be seen as beneficial.

2.5.7 List of Literature References

