2.4 Non Clinical Overview

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2.4.1 OVERVIEW OF THE NONCLINICAL TESTING STRATEGY

2.4.1.1 PHARMACOLOGICAL CLASS

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 [1, 2].

Table I: Chemical data and Identifiers of Mexiletine and 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)	
Mol. Mass	179.263 g/mol (Mexiletine) 215.721 g/mol (Mexiletine hydrochloride)	
Identifiers		
CAS number	31828-71-4 (Mexiletine) 5370-01-4 (Mexiletine hydrochloride)	
ATC code	C01BB02	
ATC Groups	*1st Level*	C: Cardiovascular System
	2nd Level	C01: Cardiac Therapy
	3rd Level	C01B: Antiarrhythmics, Class I and III
	4th Level	C01BB: Antiarrhythmics, Class Ib
PubChem	4178 (Mexiletine) 21467 (Mexiletine hydrochloride)	
IUPHAR/BPS	2629 (Mexiletine)	
DrugBank	DB00379 (Mexiletine)	
ChemSpider	4034 (Mexiletine) 20175 (Mexiletine hydrochloride)	
UNII	1U511HHV4Z (Mexiletine) 606D60IS38 (Mexiletine hydrochloride)	
KEGG	D08215 (Mexiletine) D00639 (Mexiletine hydrochloride)	
ChEMBL	ChEMBL558 (Mexiletine) CHEMBL1200606 (Mexiletine hydrochloride)	
ECHA InfoCard	100.046.190 (Mexiletine) 100.023.965 (Mexiletine hydrochloride)	

Figure 1: Chemical structure of Mexiletine (on the left) and Mexiletine hydrochloride (on the right)

2.4.1.2 SCIENTIFIC BACKGROUND

The current Application refers to Mexiletine 50 mg, 100 mg and 200 mg Capsules. The proposed products are applied under Article 10a of Directive 2001/83/EC, well established use. Mexiletine has a well "established medicinal use" within the Community for at least ten years with recognized efficacy and an acceptable level of safety.

A full justification on the Legal basis of the present application is provided in Module 1.5.1.

The proposed indications, dosage and adverse events of the products under assessment are the same as the previously licensed Mexitil by Boehringer, and more specifically for the treatment of ventricular arrhythmias which are considered as life-threatening by the physician.

Mexiletine Mexitil was approved in Europe by Boehringer as Mexiletine capsules at the strengths of 50 mg, 100 mg and 200 mg. Mexitil was available in Ireland since 1975, however it was withdrawn in 2009 purely for marketing purposes.

The proposed posology is in accordance with the SPC of Mexitil capsules:

- Loading dose: 400 mg of mexiletine
- Maintenance dose: 200-250 mg of Mexiletine three to four times daily, commencing 2 hours after the loading dose. The usual dose is between 600-800 mg in divided doses and optimal doses range from 300-1200 mg daily in divided doses.

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

In addition, mexiletine is currently licensed in different strengths in the countries presented below:

[redacted]

2.4.1.3 NON CLINICAL DEVELOPMENT PROGRAM

As mentioned in the previous section, mexiletine has a well-established use for more than 10 years within the European Union.

The present application does not include nonclinical trials as they are not required for products submitted under Article 10(a) of Directive 2001/83/EC.

[redacted]

2.4.1.4 SEARCH STRATEGY

This Nonclinical Overview examines the current state of published scientific knowledge available on the nonclinical properties and the established clinical use of the active substance aimed to justify the pharmacological and medical rationale for the proposed product and for the intended therapeutic indication.

In order to compile the Nonclinical overview, a literature review was conducted aiming to properly describe the relevant aspects regarding the pharmacology, pharmacokinetics, efficacy and safety of the under review product in humans. This literature search has demonstrated that a broad experience exists on the clinical use of the active substance for the specific indication. A survey of the pharmacological properties of the drug is provided, as well as a detailed discussion on its efficacy and safety together with its overall place in current clinical practice.

[redacted]

[redacted]

2.4.2 PHARMACOLOGY

2.4.2.1 PRIMARY PHARMACODYNAMICS

2.4.2.1.1 Mechanism of action

Mexiletine is a sodium channel blocker and further classified as a Class 1B antiarrhythmic in the Vaughan-Williams classification scheme of antiarrhythmic drugs. Mexiletine is an oral medication that blocks sodium channels in cardiac myocytes and nerve cells. Relative to cardiac myocytes, mexiletine effects phase 0 of the cardiac myocyte action potential, inhibiting the inward sodium current, and its mechanism of action can be generalized across all Class 1B anti-arrhythmics. The uniqueness of this subclass of sodium channel blockers is characterized by the type of sodium channels they best bind to and their effect on the cardiac action potential with relative changes on -ECG. To further understand the properties of the Class 1B drugs, it is important to review the cardiac myocyte action potential. The action potential is broken into five separate phases, phases 0 to 4 (Figure 2), where the sodium channels are responsible for the depolarization from the negative, approximately -85 to -90 mV, resting membrane potential to a positive depolarized state, termed phase 0 of the cardiac action potential [3]. The class 1B anti-arrhythmics bind best to sodium channels in the depolarized state. This correlates with the primary use of class 1B anti-arrhythmics and their value in ischemic arrhythmias. Ischemia causes damage to the cardiac myocytes, rendering them unable to maintain their negative resting membrane potential, producing an increased number of cardiac myocytes in the depolarized state. Moreover, the class 1B drugs have the least effect on the cardiac action potential compared to the other class 1 drugs, likely secondary to the specificity of their binding [3].

Furthermore, most Class 1 anti-arrhythmics exhibit a property called "use dependence." Use dependence is named in relation to the state of the channel that is being affected. Class 1 antiarrhythmic drugs block sodium channels best when these channels are in use, or specifically when the sodium channel is in an open or inactive state. Cardiac myocyte sodium channels are in these states more often at faster heart rates, allowing more drug to bind at these higher rates. Mexiletine exhibits use dependence by rapidly unbinding when the myocytes re-polarize and no longer remain in the depolarized state, or when the sodium channels are in a resting state (not in use). During faster heart rates, the duration between depolarized states is reduced, decreasing the time to allow the drug to unbind and increasing the time sodium channels spend in an open or inactive state, which leads to more drug bound to sodium channels, and thus having a greater effect. At slower heart rates, there is

more time between subsequent cardiac myocyte action potentials, allowing more of the drug to unbind as the sodium channels spend more time in the resting state. Simply put, use dependence means more binding at faster heart rates, and its clinical relevance is that tachycardia can be dangerous as there is an increased risk of adverse effects and toxicity at these faster rates [3].

Relative to nerve cells, blocking sodium channels disrupts the resting membrane potential, causing an inhibition of propagation of electrical impulses [3].

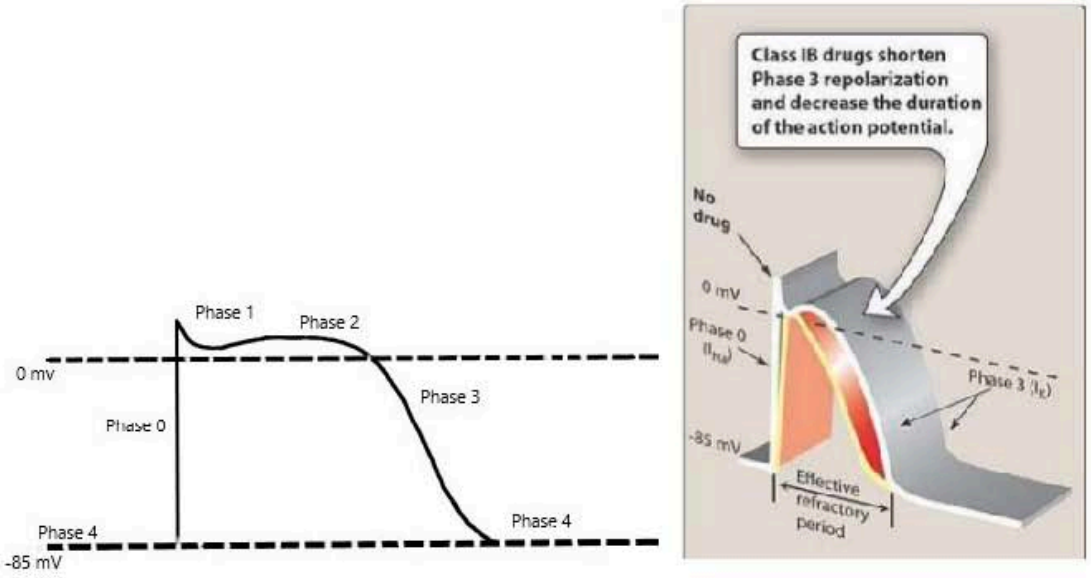


Figure 2 Cardiac Myocyte Action Potential

It is important to note, that metabolites of mexiletine were also studied, specifically meta-hydroxymexiletine (MHM). MHM is one of the metabolites of mexiletine through the CYP2D6 system. [redacted] published a paper stating the MHM can be synthesized. Additionally, they published toxicopharmacological properties on MHM and compared it to the parent compound, mexiletine, in the in vitro setting. They report that MHM possesses about two times the blocking activity of mexiletine on cardiac sodium channels, but did not impair motor coordination and showed no cytotoxicity compared to mexiletine. With the potential to have a more favourable side effect profile than mexiletine, MHM warrants further studies and research in the use of neuropathic pain and arrhythmias as a safer alternative to mexiletine [4].

2.4.2.1.2 In vitro studies

Studies in isolated myocardial cells from rat or guinea-pig ventricles using voltage clamp techniques have clearly shown blockade of the sodium current by mexiletine [5, 6]. The binding of type I anti-arrhythmic drugs to the cardiac sodium channel is saturable, reversible and occurs at pharmacologically relevant concentrations [7].

In one study in guinea-pig ventricular myocytes using a tight-seal whole cell clamp method, mexiletine produced dose-dependent reduction of the calcium current at therapeutically relevant concentrations (10 to 100 µmol/L), suggesting some blockade of calcium as well as sodium channels [8].

2.4 Nonclinical overview

In isolated atrial or ventricular muscle as well as Purkinje fibres, mexiletine acts in a very similar manner to lidocaine, reducing the maximal rate of depolarization of the action potential (V_{max}) and thus enhancing the threshold of excitability, decreasing conduction velocity and prolonging the effective refractory period [9]. [redacted] reported that mexiletine only reduced V_{max} at higher concentrations but shortened the action potential duration with a log concentration response relationship in canine Purkinje fibres, properties characteristic of the response to lidocaine. However, mexiletine reduced the effective refractory period at low concentrations while increasing it at higher concentrations, an effect which more closely resembled the changes induced by quinidine than by lidocaine [10]. Although mexiletine reduces the action potential duration and the effective refractory period, studies have consistently shown that it increases the ratio of effective refractory period to action potential duration, and this may be important to its antiarrhythmic activity.

Studies have been also performed in order to evaluate the effects of mexiletine on ischemic tissue.

The characteristic electrophysiological effects of mexiletine in isolated ventricular muscle are more prominent at higher extracellular potassium concentrations. Mexiletine may, therefore, be more effective for ventricular arrhythmias occurring in depolarized fibres, e.g. in acute myocardial ischemia. [redacted] reported that hypoxia sensitized canine Purkinje fibres to the effect of mexiletine on V_{max}, but attenuated its effect on action potential duration [11]. Furthermore, sub-endocardial Purkinje fibres in ischemic zones of canine cardiac tissue were more responsive to mexiletine than were cells from normal zones [12]. There was also an increased susceptibility for ischemic zone cells to develop re-entrant-type arrhythmias in the presence of a low concentration of mexiletine (3 mg/L). This may possibly be a result of slowed conduction due to ischemia combined with an insufficient increase in refractoriness caused by concentrations of mexiletine too low to prevent re-entry of premature responses which have already been slowed by the drug [12]. The arrhythmias were not apparent in the presence of mexiletine 6 mg/L.

In isolated perfused heart preparations, mexiletine 15 µmol/L increased the effective refractory period of ventricular tissue in the ischemic zone after occlusion-reperfusion injury and reduced the difference in repolarization time and refractoriness between tissue in normal and infarct zones [13]. Moreover, it reduced the incidence of ventricular fibrillation (VF) after programmed electrical stimulation (PES) and inhibited ventricular tachyarrhythmias after hypoxia-reoxygenation or ischemia-reperfusion [13].

Mexiletine has dose dependent anticonvulsant properties in both mice and rats, protecting the animals from both electroshock and pentylenetrazole induced convulsions. The maximum protective effect of mexiletine under these experimental conditions was obtained within 15 minutes after oral and within I minute after intravenous administration. The effect disappeared 6 hours after oral, and was reduced to 20 %, 4 hours after intravenous, administration [9].

Mexiletine appears to exert a biphasic action on the central nervous system under these experimental conditions. In the lower dose range (1 to 3mg/kg) intravenous mexiletine produced no EEG changes but prolonged the duration of after discharges following electric stimulation of both the hippocampus and amygdaloid regions. At higher doses (10 mg/kg, IV) there were signs of central nervous system depression with shortened duration of after discharges recorded at various cerebral sites [9].

The latest study [redacted] examined the broad antiarrhythmic effect of mexiletine in different arrhythmia models using isolated rabbit hearts. 12 rabbit hearts were used to examine potential antiarrhythmic effects of mexiletine in atrial fibrillation (AF). The results showed that mexiletine exerts a universal antiarrhythmic effect in different arrhythmia models in isolated rabbit

hearts. Mexiletine effectively reduced the occurrence of torsade de pointes in pharmacological models of LQT2 and LQT3. In addition, mexiletine eliminated ventricular arrhythmias in an established model of SQTS. Furthermore, mexiletine also effectively reduced inducibility of atrial fibrillation in isolated hearts [14].

2.4.2.1.3 In vivo studies

An early study [redacted]. examined the antiarrhythmic effects of mexiletine or KO 1173 and showed suppression of various kinds of experimental arrhythmias [15, 16]. Mexiletine was effective in canine ventricular arrhythmias induced by digitalis. By intravenous infusion at 0.2 mg/kg per min and at a plasma concentration of 0.6 pg/ml, mexiletine restored sinus rhythm. In the canine 24-hr two-stage coronary ligation arrhythmia, intravenous infusion of mexiletine, 0.2 to 0.4 mg/kg per min, restored sinus rhythm at a plasma concentration of 5.3 pg/ml. Arrhythmias induced by halothane and epinephrine in dogs were abolished by either mexiletine (0.6 mg/kg i.v.), phenytoin (1.1 mg/kg), or procainamide (4.1 mg/kg) [15, 16].

Antiarrhythmic effects of mexiletine were examined in here canine ventricular arrhythmia models in dogs-digitalis, adrenaline and two-stage coronary ligation-induced arrhythmias. The minimum effective plasma concentration for each arrhythmia model was determines. As presented in Table III, mexiletine suppressed all the arrhythmias.

Table III Antiarrhythmic profile of mexiletine on canine ventricular arrhythmia models [17]

Canine minimum antiarrhythmic plasma concentration (μg/ml)	*Digitalis arrhythmia*	1.8
	Coronary ligation arrhythmia	1.9
	Epinephrine arrhythmia	3.7
Canine membrane- stabilizing concentration in vitro (μg/ml)		2

The minimum effective plasma concentrations of mexiletine in experiments involving digitalis- or 24- and 48-hr coronary ligation-induced arrhythmias were 1.8 + 0.6, 1.9 ± 0.3, and 2.2 ± 0.4 μg/ml, respectively. These concentrations were significantly lower than those in epinephrine-induced arrhythmia, 3.7 ± 1.9 μg/ml [17]. This finding indicates that mexiletine is less effective in epinephrine induced arrhythmias, probably because it has no β-adrenoceptor blocking activity [18], and does not contradict the results [redacted], who found that mexiletine is more effective than phenytoin and procainamide .

[redacted] reported that enantiomers of mexiletine 20 mg/kg i.v., had little effect on ischemia-induced ventricular fibrillation in conscious or anaesthetized rats. In conscious rats 20 mg/kg caused convulsions in 78 – 89 % of rats when the plasma concentration of racemate was 20 +2 μM. In anaesthetized animals a higher dose (40 mg/kg) of racemate could be given; this completely prevented ischemia-induced fibrillation when the plasma concentration was 26 + 2 μM. Racemate and enantiomers accumulated in the heart and brain of conscious animals to give tissue:plasma ratios of 7.5 and 23, respectively. With electrical stimulation, both racemate and enantiomers dose dependently (4 - 32 mg/kg) increased threshold currents for induction of ventricular fibrillation, increased refractory period and minimally changed the ECG. This study failed to show major differences between racemate or enantiomers except for consistently lower (20 – 30 %) plasma concentrations of R-(-) at all dose levels. Therefore the authors concluded that mexiletine prevented ischemia-induced ventricular fibrillation in anaesthetized animals but only when given at doses producing convulsions in conscious animals [19].

2.4.2.2 SECONDARY PHARMACODYNAMICS

2.4.2.2.1 In vivo studies

The effects of mexiletine on thermal allodynia and hyperalgesia in diabetic mice have been studied by several authors. Tail-flick latencies at heat intensity of 35 and 50 V in diabetic mice were shorter than those in non-diabetic mice. In diabetic mexiletine increased the tail-flick latency at 35 V to the level observed in non-diabetic mice. The results [redacted] suggested that the mexiletine-induced antinociception in diabetic mice involves the inhibition of the nociceptive transmission of capsaicin-sensitive primary fibres [20]. The same group later suggested that i.p. pre-treatment with mexiletine produced dose-dependent inhibition of fenvalerate-induced hyperalgesia and allodynia in mice, especially diabetic mice. This effect was, at least in part, mediated by the inhibition of TTX-R sodium channel-mediated nociceptive transmission in the spinal cord [21]. The same also group has suggested that δ_1-opioid receptor-mediated mechanisms may be involved in the antinociceptive effect of mexiletine [22]. When the effects of mexiletine on vincristine-induced thermal hyperalgesia in mice were studied, it was demonstrated that systemic mexiletine can effectively attenuate vincristine-induced thermal hyperalgesia and the blockade of nitric oxide-induced enhancement of nociceptive transmission, in which tetrodotoxin-resistant sodium channels play an important role, may participate in the antinociceptive effect of mexiletine on vincristine-induced thermal hyperalgesia [23].

The effect of spinal administration of mexiletine (10 - 1000 mg) on the spontaneous and peripherally evoked responses of spinal neurones of nerve injured (selective ligation of spinal nerves L5-L6; SNL) rats were examined [redacted] A high proportion of the spinal neurones of SNL rats exhibited de novo spontaneous activity (mean frequency of firing 4 ± 1 Hz) and this activity was highly sensitive to spinal mexiletine ($F_{5,55}$= 2.5, P ≤ 0.05). The spinal neurones of the sham operated rats exhibited negligible spontaneous activity. The electrically evoked Aβ-fibre neuronal responses of SNL and sham operated rats were not significantly influenced by spinal mexiletine. In contrast, the Aδ-fibre and C-fibre evoked neuronal responses of the SNL rats, but not sham operated rats, were significantly reduced by spinal mexiletine ($F_{5,52}$= 4.9, P ≤ 0.001 and $F_{5,48}$= 12, P ≤ 0.0001, respectively). In addition, the mechanical punctate von Frey 9 and 50 g evoked neuronal responses of the SNL rats, but not sham operated rats, were significantly reduced by spinal mexiletine ($F_{5,57}$= 4.3, P ≤ 0.002 and $F_{5,52}$= 6.1, P ≤ 0.001). these data suggest that following nerve injury there is a mexiletine sensitive spinal substrate which contributes to Aδ-fibre and C-fibre, but not Aβ-fibre, somatosensory transmission [24].

Mexiletine at 10 and 30 mg/kg, s.c. doses, produced a significant and dose-dependent inhibition of CCI-induced static and dynamic allodynia on day 14 post-surgery in rats [25].

In infected with herpes virus BALB/C mice, the antinociceptive effect of mexiletine (at dose of 5.0 mg/kg) attained peaks at 60–90 min after administration and declined gradually to non-treated levels by 150 min. Intraperitoneal administration of mexiletine at a dose of 17.5 mg/kg (but not 10.0 mg/kg) caused significant increase in β-endorphin levels in the mid brain and hypothalamus of HSV-inoculated mice. However, mexiletine scarcely affected noradrenaline (norepinephrine) levels in the pons and medulla oblongata, even when HSV-inoculated mice were treated with 17.5 mg/kg mexiletine. These results strongly suggested that mexiletine exerts antinociceptive effects on herpes-related pain through enhancement of β-endorphin levels in the central nervous system in HSV-inoculated mice [26].

Mexiletine was used also successfully used for treating neuropathic pain in peripheral neuropathy. The experiment was conducted with 60 male Wistar rats. The constriction nerve injury (CCI) rats were given an intravenous injection of normal saline and mexiletine (5 or 15 mg/kg). Mexiletine significantly suppressed spontaneous firing frequency, an on-off firing pattern that consisted of cyclic bursting spikes and ectopic firing generation under the hypoxic condition. Mexiletine suppressed ectopic firing by blocking activity of the abnormal sodium channel at the nerve-injured site and dorsal root ganglion without blocking nerve conduction [27].

2.4.2.3 SAFETY PHARMACOLOGY

2.4.2.3.1 Central nervous system

In conscious beagles, mexiletine has stimulatory effect on the central nervous system [18, 28, 29]. Stronger central excitatory effects, including tonic and clonic seizures, were induced by lidocaine, 10 mg/kg i.v. [30]. The CNS side effects of mexiletine were weaker than those of lidocaine.

2.4.2.3.2 Cardiovascular system

Knowledge of the general pharmacology and toxicology of mexiletine in animals is important for the safe and efficient clinical use of mexiletine. Intravenous mexiletine (3 - 5 mg/kg) decreased the heart rate in all three models of canine arrhythmias, as described [redacted]. In conscious beagle dogs with coronary ligation arrhythmia, the antiarrhythmic dose of mexiletine did not change the atrial rate, which was recorded directly from the left atrial appendage and presumably reflected the sinoatrial node activity. Bradycardia, a transient decrease in the atrial rate, was induced by mexiletine only in the digitalized dog [17]. Absence of bradycardia in two other experimental groups indicates that mexiletine is not a strong depressant on the normal sinoatrial node. At 5 mg/kg, mexiletine lowered the blood pressure transiently. This transient hypotensive effect of mexiletine was also observed in dogs with halothane/epinephrine-induced arrhythmias. Though the mechanism of hypotension is not known, mexiletine has a vasodilatory effect, and by intra-arterial injection it dilates coronary arteries [32].

The vasodilatory effect of mexiletine and slight suppression of the sinoatrial node activity were observed after intravenous injection of the drug. By oral administration, mexiletine did not produce hypotension at doses that suppressed arrhythmias caused by coronary artery ligation [17].

Except for patients with sick sinus syndrome, mexiletine has little effect on the spontaneous frequency of the sinoatrial node or on the recovery time following overdrive suppression [33, 34]. Mexiletine had no effect on Ca^{2+} currents or atrioventricular conduction. At higher doses, however, the drug increased intraventricular conduction time and the refractory period [32-34].

Mexiletine has been shown to decrease blood pressure and myocardial contractility and to induce bradycardia [30]. In a clinical situation, there are few reports of hypotension after intravenous mexiletine [35]. However, in patients without serious myocardial decompensation, hypotension after intravenous injection of mexiletine was not seen [34]. Oral mexiletine can, therefore, be given to most patients without cardiovascular depression. But when the drug is used in patients suffering from acute myocardial infarction, it must be borne in mind that mexiletine has negative inotropic and vasodilator actions.

[redacted]

2.4.2.4 PHARMACODYNAMIC DRUG INTERACTIONS

Where there is concurrent administration of mexiletine and some other anti-arrhythmic drugs, an increased effect on conduction and pumping of the heart is to be expected. Mexiletine may be used concurrently with the cardiovascular drugs digoxin, amiodarone, quinidine and beta-adrenergic blocking agents [36].

Concomitant administration of mexiletine with warfarin may increase the risk of bleeding [36].

Local anaesthetic toxicity may occur in patients who receive mexiletine and local anaesthetic agents concurrently [37].

2.4.3 PHARMACOKINETICS

The pharmacokinetics of mexiletine are summarized in the following table (Table IV) [38].

Table IV Kinetic disposition of mexiletine enantiomers in rats (n=6) treated with a single dose of the racemic drug

Parameter	R-(-)-Mexiletine	S-(+)-Mexiletine
C_{max} (ng/ml)	71.62 [102.25 (52.51–257.02)]	157.74 [188.10 (50.89–325.32)]
t_{max} (h)	0.38 [0.37 (0.20–0.53)]	0.42 [0.54 (0.15–0.93)]
AUC_{0-inf} (ng h/ml)	180.65 [224.94 (59.78–390.09)]	307.22 [412.26 (118.87–705.64)]
$t_{½}$ a (h)	0.09 [0.13 (0.03–0.28)]	0.13 [0.25 (0.01–0.59)]
α (h^{-1})	0.76 [1.15 (0.49–2.78)]	0.78 [0.85 (0.54–1.17)]
β (h^{-1})	0.23 [0.20 (0.10–0.51)]	0.17 [0.18 (0.01–0.35)]
$t_{½}$ α (h)	1.07 [0.99 (0.01–1.99)]	0.89 [0.99 (0.51–1.48)]
$t_{½}$ β (h)	2.95 [4.84 (4.83–14.50)]	4.35 [14.16 (5.81–34.14)]
CL/F (L h^{-1} kg^{-1})	27.76 [25.04 (12.02–38.05)]	16.29 [17.43 (6.60–28.25)]
Median, mean and (CI 95 %), n 5=6 for each time		

2.4.3.1 ABSORPTION

Mexiletine is rapidly and completely absorbed after oral administration. Oral bioavailability ranges from 80 to 88 percent and intramuscular availability is virtually 100 % [39]. Membrane (pH 6.5 and 7.4) permeability coefficient has been calculated for mexiletine [40]. P_m for pH 6.5 has been determined to be 818 × 10^{-6} cm s^{-1} and 6,385 × 10^{-6} cm s^{-1}.

The pharmacokinetics of mexiletine (both R and S enantiomers) were evaluated [redacted] in male Wistar rats after oral administration and results and concentration-time profiles are presented in Figure 3.

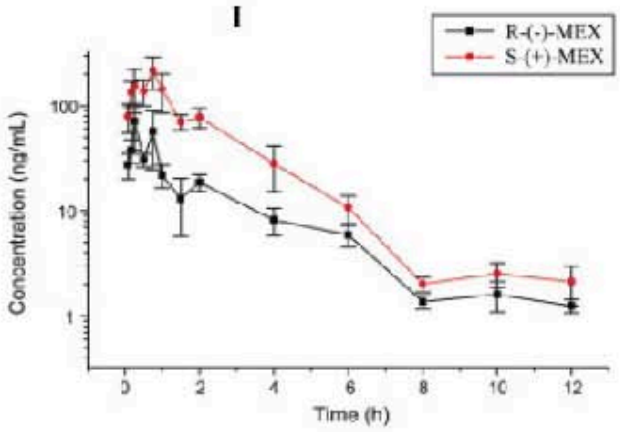


Figure 3 Plasma concentration versus time curves for Mexiletine enantiomers [38]

2.4.3.2 DISTRIBUTION

The kinetics of distribution of the enantiomers of mexiletine have been studied in various tissues (heart, brain, lungs, liver, kidneys and fat) in male Sprague-Dawley rats after administration of a single i.v. dose (10 mg/kg) of racemic mexiletine. The pharmacokinetic parameters calculated from the serum data showed a 32 % greater systemic clearance (162 ml/min/kg vs 123 ml/min/kg) and a 22 % greater steady-state volume of distribution (90 L/kg vs 7.4 L/kg) for R-(-)-mexiletine relative to the S-(+)-enantiomer. However, the terminal elimination half-lives of the enantiomers (1.4 and 1.3 h for R(-)- and S(+)-mexiletine, respectively) did not exhibit stereoselectivity [41].

Maximum tissue concentrations of the enantiomers were observed at 5 min after dosage in all tissues studied. Stereoselective uptake was evident only in the liver tissue and was 2.4-fold greater for S (+)-mexiletine. High tissue/serum ratios (> 20 for both enantiomers) were observed in lungs, brain and kidneys. The cardiac concentrations of R(-)- and S(+)-mexiletine were 8- and 7-fold those of serum, respectively and these results demonstrated that the uptake of mexiletine enantiomers into the target tissue (heart) is not stereoselective [41].

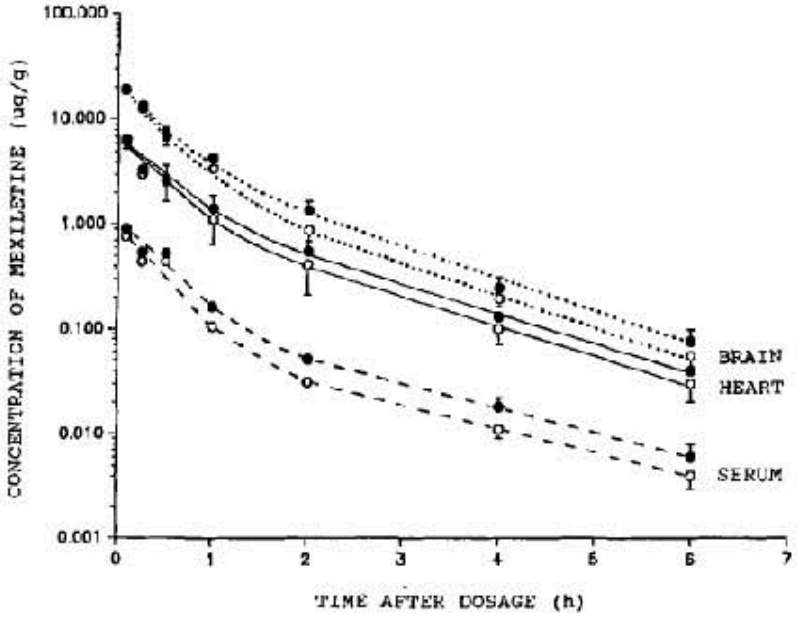


Figure 4 Concentration-time profiles of mexiletine enantiomers in serum, heart and brain tissues. Dose of racemic mexiletine (10 mg/kg) was administered intravenously. Values are means ± SD of results from four or five rats. •-S(+) Mexiletine and O- R(-) Mexiletine [41]

Table V Pharmacokinetic parameters of mexiletine enantiomers calculated from tissue concentration-time data after a single i.v. dose of racemic mexiletine [41]

Tissue	Enantiomer	$T_{1/2}$ (β) (h)	AUC_t (µg h/g)	Ratio of tissue/serum concentration
Heart	R(-)-Mexiletine	1.1	4.4	8
	S(+)-Mexiletine	1.1	5.1	7
Brain	R(-)-Mexiletine	1.0	11.9	25
	S(+)-Mexiletine	1.0	14.0	21
Liver	R(-)-Mexiletine	1.1	2.0	4
	S(+)-Mexiletine	1.2	4.4	8
Lungs	R(-)-Mexiletine	1.0	22.4	32
	S(+)-Mexiletine	1.0	27.1	28
Kidneys	R(-)-Mexiletine	1.1	11.1	26
	S(+)-Mexiletine	1.0	13.6	22
Fat	R(-)-Mexiletine	0.7	1.3	1
	S(+)-Mexiletine	0.7	1.5	1

2.4.3.3 METABOLISM

Mexiletine undergoes extensive hepatic metabolism. The major metabolites, hydroxymethyl mexiletine, parahydroxy mexiletine, and their corresponding alcohols do not seem to demonstrate significant antiarrhythmic activity [42].

The major metabolites of mexiletine are presented in Figure 5, [redacted]

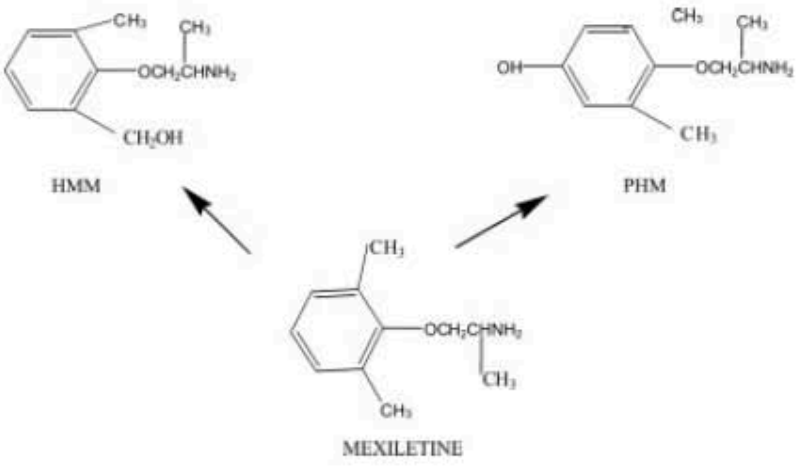


Figure 5 Major metabolic pathways of Mexiletine [38]

Human livers have been used for the investigation of mexiletine biotransformation in vitro. The major metabolic pathways of mexiletine oxidation to form hydroxymethylmexiletine (HMM) and p-hydroxymexiletine (PHM) were characterized in liver cell preparations. The localization of reactions in the microsomal fraction, their heat lability, NADPH requirement and inhibition by prototype cytochrome P450 inhibitors implied that they were catalysed by P450. Additionally, there was a very strong correlation between V_{max} values for both reactions and these results, coupled with a parallel effect of inhibitors on HMM and PHM formation, argue that both reactions are mediated by a common P450 or closely related isoenzymes [43].

Vandamme et al compared the metabolism of the two stereoisomers of mexiletine in vitro in human liver microsomes. Parahydroxylation (aromatic hydroxylation) was favored for S(+)-mexiletine with a mean intrinsic clearance higher than for R(-)-mexiletine. The R(-) enantiomer exhibited a threefold higher mean V_{max} value for aliphatic hydroxylation than S(+)-mexiletine, concluding that hydroxylation reactions of mexiletine exhibit stereoselectivity in vitro in human liver microsomes and are catalyzed by P450IID6 [44].

The study [redacted] identified N-hydroxymexiletine glucuronide and suggested that this metabolite corresponds to a mexiletine acid-labile conjugate [45].

2.4.3.4 EXCRETION

Mexiletine is predominantly metabolized by the liver with < 15 % of the parent compound excreted as unchanged drug in the urine [39, 42]. However, the amount of mexiletine excreted renally is highly dependent on urinary pH. In an acid urine (pH = 5), almost 50 % of mexiletine may appear in the urine as unchanged parent compound and the elimination half-life may be as brief as three hours [46, 47]. Likewise, an alkaline urine may increase the elimination half-life. The usual total body clearance ranges from 6.5 - 10.3 ml/min/kg [39].

2.4.3.5 PHARMACOKINETIC DRUG INTERACTIONS

All medicines that affect gastrointestinal movement may affect the absorption of oral mexiletine. Drugs that delay gastric-emptying (e.g. opiates, antacids and atropine) may delay the absorption of mexiletine [48]. Similarly, drugs that accelerate gastric-emptying (e.g. metoclopramide) will reduce the time to peak mexiletine concentrations and increase peak concentrations [48].

Since mexiletine is metabolized mainly in the liver, substances that influence liver enzyme function may alter the concentration of mexiletine in the blood. In particular, interactions with the two cytochrome P450 isozymes CYP1A2 and CYP2D6 have to be considered. It may be necessary to reduce the dose of mexiletine in cases of concomitant administration of substances that lead to enzyme inhibition in the liver. In cases of concurrent therapy with substances that lead to enzyme induction it may be necessary to increase the dose of mexiletine since it is metabolized at a faster rate [49].

Concurrent administration of mexiletine may increase plasma levels of theophylline [49, 50] and caffeine [48].

Drugs which markedly acidify or alkalise urine should be avoided because they may enhance or reduce, respectively, the rate of drug excretion and correspondingly affect the plasma concentration of mexiletine [46].

2.4.3.6 OTHER PHARMACOKINETIC STUDIES

No other relevant pharmacokinetic studies were retrieved from the public domain.

2.4.4 TOXICOLOGY

The toxicity of mexiletine hydrochloride has been evaluated in animal species, following acute, sub-chronic and chronic administration. Carcinogenicity, reproduction and mutagenicity studies have also been performed.

2.4.4.1 SINGLE-DOSE TOXICITY

The following toxicity values have been reported for mexiletine hydrochloride (Table VI) and mexiletine (Table VII) after administration by different routes.

Table VI Acute Toxicity of Mexiletine hydrochloride [51-53]

Species	Test type	Route	Reported Dose (Normalized Dose)	Effect	Ref.
Dog	LD_{50}	Oral	356 mg/kg (356 mg/kg)	NR	As cited in [51]
		IV	19 mg/kg (19 mg/kg)	NR	
		Oral	112 mg/kg	NR	[53]
		IV	40-60 mg/kg	NR	
		SC	65-88 mg/kg	NR	
Mouse	LD_{50}	IM	128 mg/kg (128 mg/kg)	**Behavioural:** Altered SLEEP time (including change in righting reflex) **Behavioural:** Convulsions or effect on seizure threshold	As cited in [51]

2.4 Nonclinical overview

Species	Test type	Route	Reported Dose (Normalized Dose)	Effect	Ref.
				Lungs, Thorax, or Respiration: Respiratory stimulation	
		IP	114 mg/kg (114 mg/kg)	NR	
		IV	21 mg/kg (21 mg/kg)	NR	
		Oral	272 mg/kg (272 mg/kg)	**Sense organs and special senses:** Mydriasis (Pupillary dilation): Eye **Behavioural:** Changes in motor activity (specific assay) **Gastrointestinal:** Changes in structure or function of salivary glands	
		SC	235 mg/kg (235 mg/kg)	**Behavioural:** Ataxia **Musculoskeletal:** Other changes **Behavioural:** Convulsions or effect on seizure threshold	
		Oral	260 mg/kg	NR	[53]
		SC	170 mg/kg	NR	
Rabbit	LD_{50}	Oral	160 mg/kg (160 mg/kg)	**Sense organs and special senses: other:** Eye **Lungs, thorax, or respiration:** Respiratory stimulation **Behavioural:** Convulsions or effect on seizure threshold	As cited in [51]
		Oral	450 mg/kg	NR	[53]
Rat	LD_{50}	Oral	330 mg/kg (330 mg/kg)	**Behavioural:** Tremor **Behavioural:** Somnolence (general depressed activity) **Behavioural:** Ataxia	As cited in [51]
		IV	27 mg/kg (27 mg/kg)	**Behavioural:** Convulsions or effect on seizure threshold **Lungs, thorax, or respiration:** Respiratory stimulation **Behavioural:** Tremor	
		IM	190 mg/kg (190 mg/kg)	**Lungs, thorax, or respiration:** Respiratory stimulation **Behavioural:** Tremor **Behavioural:** Convulsions or effect on seizure threshold	
		SC	500 mg/kg (500 mg/kg)	**Behavioural:** Tremor **Musculoskeletal:** Other Changes **Behavioural:** Somnolence (general depressed activity)	
		Oral	630 mg/kg	NR	[53]
		IV	720 mg/kg	NR	
Women	TDLo	Oral	360 mg/kg (360 mg/kg)	**Behavioural:** Convulsions or effect on seizure threshold **Behavioural:** Coma **Lungs, thorax, or respiration:** Dyspnoea	[52]

Table VII Single dose toxicity data for Mexiletine [54]

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect
Human	LDLo	Oral	63 mg/kg (63 mg/kg)	**Lungs, Thorax, or Respiration:** Cyanosis **Behavioural:** Convulsions or Effect on Seizure Threshold **Gastrointestinal:** Nausea or Vomiting
Man	TDLo	Oral	349 mg/kg/4D-I (349 mg/kg)	**Blood:** Thrombocytopenia
Man	LD_{50}	Intraperitoneal	114 mg/kg (114 mg/kg)	**Cardiac:** Arrhythmias (including changes in conduction)
Man	LD_{50}	Intravenous	23 mg/kg (23 mg/kg)	NR
Man	LD_{50}	Oral	320mg/kg (320 mg/kg)	
Rat	LD_{50}	Intravenous	41 mg/kg (41 mg/kg)	

2.4.4.2 SUB-CHRONIC AND CHRONIC TOXICITY STUDIES

Sub-chronic oral toxicity studies were performed in mice for 4 weeks and at doses of 40, 80 and 160 mg/kg, in rats for 4 weeks at doses of 40, 100 and 250 mg/kg, in rats also for 13 weeks at doses of 15, 30, 60 and 150 - 200 mg/kg and in dogs for 13 weeks at doses of 3, 9 and 15 - 30 mg/kg [53].

In the 4-week mouse and rat studies, doses of 80 and 100 mg/kg, respectively, produced slight transient ataxia and convulsions. In male mice, myocardial necrosis (3/25) and deaths (4/25) were recorded at the highest dose level. In rats, a reversible decrease in total protein, increase in cholesterol and a slight increase in liver weights (females only) were noted in the high dose group. However, no significant pathological findings were observed. In the 13-week rat study, no clinical signs of intolerance other than a slight reduction in mean food consumption in the high-dose males were observed. Histopathological examination revealed fatty changes in the livers of animals in the two highest dosage groups, which appeared to be largely reversible in recovery animals. In the 13-week dog study, diarrhoea and emesis were the only symptoms noted. Histopathological examination showed a fatty degeneration of myocardial fibres in 2/6 middle-dose and 4/6 high-dose animals and peripheral fatty degeneration of the liver in 1/6 high-dose animals [53].

Sub-chronic intravenous studies of 4 weeks duration were also conducted in dogs (at doses of 1.5, 3, and 13.5 mg/kg), monkeys (at doses of 1.5, 4.5 and 12.0 mg/kg) and rats (at doses of 5, 10 and 20 mg/kg). In the dog and monkey, doses of 12 and 13.5 mg/kg produced muscular incoordination, ataxia and convulsions. A transient increase in heart rate was also noted in dogs. In rats, dosages of 10 and 20 mg/kg caused ataxia, tonic spams, hyperventilation and mortalities (two deaths occurred at 10 mg/kg and 17 (57 %) at 20 mg/kg. however, in all three species histopathological examination failed to indicate any treatment-related findings [53].

Chronic oral toxicity studies were conducted in rats and dogs. Three studies were performed in rats: two of 26-weeks duration at doses of 20, 40, 80 and 120 mg/kg (gavage) and 40, 90 and 200 mg/kg

(diet), respectively; and one of 78-weeks duration at doses of 20, 40 and 240 mg/kg (diet). Following oral administration to rats at doses of 80 mg/kg and higher, effects on the central nervous system were observed which included ataxia and convulsions. Other effects included decreased food consumption, weight loss, fatty livers and mortalities. Reversible increase in organ weights were also noted. In the 78-week study, elevations in SGPT and serum alkaline phosphatase values were observed in the high-dose group, but were not associated with any histopathological findings [53].

In the dog, oral studies of 27 and 52 weeks duration were conducted at dose levels of 5, 10, 20 and 40 mg/kg. Except for an increased incidence of emesis, the 20 mg/kg dose level was well tolerated in both the 27 and 52 week studies. At the high dose (40 mg/kg), ataxia, tremors, salivation and tonic-clonic convulsions were observed. In the 52-week study, a transient increase in heart rate was also noted and three of the six high-dose animals died (after 36 weeks). Histopathological examination of animals in the 27-week study revealed fatty changes in the heart in the two low-dose groups (2/6 animals at 5 mg/kg, 1/6 at 10 mg/kg) and in the liver in the two high-dose groups (1/6 animals at 20 mg/kg and in 4/6 at 40 mg/kg). In the 52-week study, fatty changes were observed in the livers of 1/6 controls, 2/6 low and 2/6 mid-dose dogs. These changes were not observed in the high-dose group [53].

2.4.4.3 GENOTOXICITY AND CARCINOGENICITY

The most recent review [redacted] included all the information retrieved on carcinogenicity in animals and humans of 535 marketed pharmaceuticals whose expected clinical use is continuous for at least 6 months or intermittent over an extended period of time. As reported [redacted], in the long-term carcinogenesis assay in mice, the result was negative for mexiletine [55].

2.4.4.4 CARCINOGENICITY

An 18-month oral carcinogenicity study in mice and a two-year study in rats did not established a carcinogenic potential for mexiletine hydrochloride at doses up to 160 and 240 mg/kg, respectively, which is 7 to 10 times the maximum recommended human daily dose. Anaemias and abnormally low WBC levels were seen sporadically in treated rats. High dose male rats exhibited fatty liver changes at twice the rate of controls [53].

2.4.4.5 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

2.4.4.5.1 Fertility

Effects of mexiletine on fertility and general reproductive performance were determined in rats; teratogenic potential was evaluated in mice, rats and rabbits following oral administration of up to 200 mg/kg (approximately 8 times the maximum recommended human daily dose), no effect on fertility was noted. However, drug-treated animals exhibited slight ataxic movements, tremors and weakness immediately post-dosing. Although high dose levels produced side effects in dams, there were no effects no effects on litter parameters or on the development, behaviour, function or reproductive capability of foetuses or second generation. Similarly, oral doses of up to 60 mg/kg administered during gestation and throughout lactation were without effect on litter parameters or progeny. Although segment II studies via the oral route of administration in 3 species failed to reveal a teratogenic potential at doses of up to 80 mg/kg/day, these studies suggested an increased sensitivity to the convulsant action of mexiletine with pregnancy. Rat and rabbit intravenous administration studies at doses up to 10 mg/kg also did not result in any teratogenic effects, although rabbits in the

middle-dose group (7 dead implants among 14 pregnant animals in the control group, 8/13 at 2.5 mg/kg, 15/15 at 5 mg/kg, 4/15 at 10 mg/kg) suggested a reduced viability at these levels [53].

Additionally, mexiletine hydrochloride did not induce any mutagenic effects in the Ames test, with or without microsomal enzyme activation, at concentrations of 3.2 - 3000 µg/plate [53].

2.4.4.5.2 Pregnancy and Lactation

Mexiletine crosses the placenta. Although teratogenicity has not yet been linked to mexiletine and reports demonstrating the drug's successful use in women during pregnancy exist [56, 57], data during pregnancy are limited [56]. Mexiletine has been categorized (FDA Category) as Class C drug, i.e. studies in pregnant women are lacking and animal studies are either positive for foetal risk or lacking as well [58].

2.4.4.6 LOCAL TOLERANCE

Not applicable since oral administration applies for Mexiletine capsules.

2.4.4.7 OTHER TOXICITY STUDIES

2.4.4.7.1 Excipients

The proposed products contain the following excipients:

- Maize starch
- Colloidal Silicon Dioxide
- Magnesium Stearate

The pharmaceutical excipients are well known and commonly used in the pharmaceutical industry and fulfil the requirements of Ph. Eur or BP.

2.4.4.7.1.1 Maize starch

Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant [59].

As a diluent, starch is used for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix [redacted], and to improve powder flow, especially when using dried starches. Starch [redacted] can act as an anti-adherent and lubricant in tableting and capsule filling.

In tablet formulations, freshly prepared starch paste is used [redacted] as a binder for wet granulation. [redacted]

Starch is one of the most commonly used tablet disintegrants [redacted]

[redacted]

Starch is an edible food substance, considered a food ingredient and not a food additive. It is regarded as an essentially nontoxic and non-irritant material. Starch is therefore widely used as an excipient in pharmaceutical formulations.

[redacted]

Allergic reactions to starch are extremely rare and individuals apparently allergic to one particular starch may not experience adverse effects with a starch from a different botanical source. The wheat proteins (gluten) are problematic for conditions such as celiac disease.

Contamination of surgical wounds with the starch glove powder used by surgeons has resulted in the development of granulomatous lesions [68].

Reported LD_{50} values [69]:

- LD_{50} (Mouse, IP): 6.6 g/kg

2.4.4.7.1.2 Colloidal Silicon Dioxide

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders [70] in a number of processes such as tableting [71] and capsule filling [72].

Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations [73]. With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity.

Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and non-irritant excipient. However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide should therefore not be administered parenterally.

Reported LD_{50} values [74]:

- LD_{50} (Rat, IV): 0.015 g/kg
- LD_{50} (Rat, oral): 3.16 g/kg

2.4.4.7.1.3 *Magnesium Stearate*

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture [redacted]. It is also used in barrier creams [75].

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation [75].

No toxicity information is available relating to normal routes of occupational exposure. Limits for heavy metals in magnesium stearate have been evaluated in terms of magnesium stearate worst-case daily intake and heavy metal composition [76].

Toxicity assessments of magnesium stearate in rats have indicated that it is not irritating to the skin, and is nontoxic when administered orally or inhaled [77, 78].

Magnesium stearate has not been shown to be carcinogenic when implanted into the bladder of mice [79].

Reported LD_{50} values [80]:

- LD_{50} (Rat, inhalation): > 2 mg/L
- LD_{50} (Rat, oral): > 10 g/kg

[redacted]

[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]

The chemical structure of Mexiletine impurities are presented in Table IX.

Table IX Chemical structure of Mexiletine impurities

Impurity	Chemical name of Impurity	Chemical structure
Impurity A	[redacted]	[redacted]
Impurity C	[redacted]	
Impurity D	[redacted]	

2.4.4.7.2.1 *Justification of known Impurities*

The limits of Impurity A and Impurity C have been set in line with the British Pharmacopoeia monograph "Mexiletine capsules".

The limit of Impurity D has been set according to the ICH Guideline Q3B (R2) on Impurities in new drug products. [redacted]

2.4.4.7.2.2 *Justification of any unknown Impurities*

According to the ICH Guideline Q3B (R2) the identification threshold considering a maximum daily dose [redacted]

2.4.4.7.2.3 *Justification of Total Impurities*

The limit set for total impurities is in accordance with the British Pharmacopoeia monograph "Mexiletine Capsules".

2.4.5 INTEGRATED OVERVIEW AND CONCLUSIONS

Mexiletine is a local anesthetic antiarrhythmic agent whose chemical structure and electrophysiological properties closely resemble those of lignocaine although its anticonvulsant and pharmacokinetic properties differ from that drug.

The electro physiological properties and antiarrhythmic activity of mexiletine have been extensively investigated in isolated cell preparations, in intact tissue in vivo and in clinical studies. Thus, mexiletine,

orally or intravenously, has little influence on haemodynamic variables either in healthy individuals or patients with cardiac disease.

Mexiletine is administered as a racemic mixture of equal parts of the R (-) and S (+) enantiomers and its bioavailability has been reported to be 80 - 88 %.

The toxicological studies are limited, however, mexiletine has not been proved to be mutagenic or carcinogenic and cannot significantly affect the reproduction in various animal models studied.

As described in the relevant sections of the present documents, mexiletine has a well-established use for over 40 years. The studies included in this document can support the well-known pharmacokinetic, pharmacodynamic and safety profile of the product.

The characteristics of mexiletine are adequately reflected in the SmPC and the indications and precautions for the use of this medicinal product are justified by its pharmacological properties.

Based on the extensive analysis of literature data, it can be stated that the pharmacology and toxicity of mexiletine are well known with the non-clinical safety profile being acceptable for the proposed indications. It is unlikely that the use of mexiletine represents any significant risk and further toxicological studies are not deemed necessary.

The benefit-risk profile of mexiletine is considered to be favourable, provided that the product is used according to the SmPC.

Overall, it can be stated that the investigations performed on mexiletine cover all aspects of safety assessment required and can therefore demonstrate an acceptable level of safety for mexiletine under the conditions stipulated in the SmPC and marketing authorisation should be granted for mexiletine.

[redacted]

2.4 Nonclinical overview

[redacted]

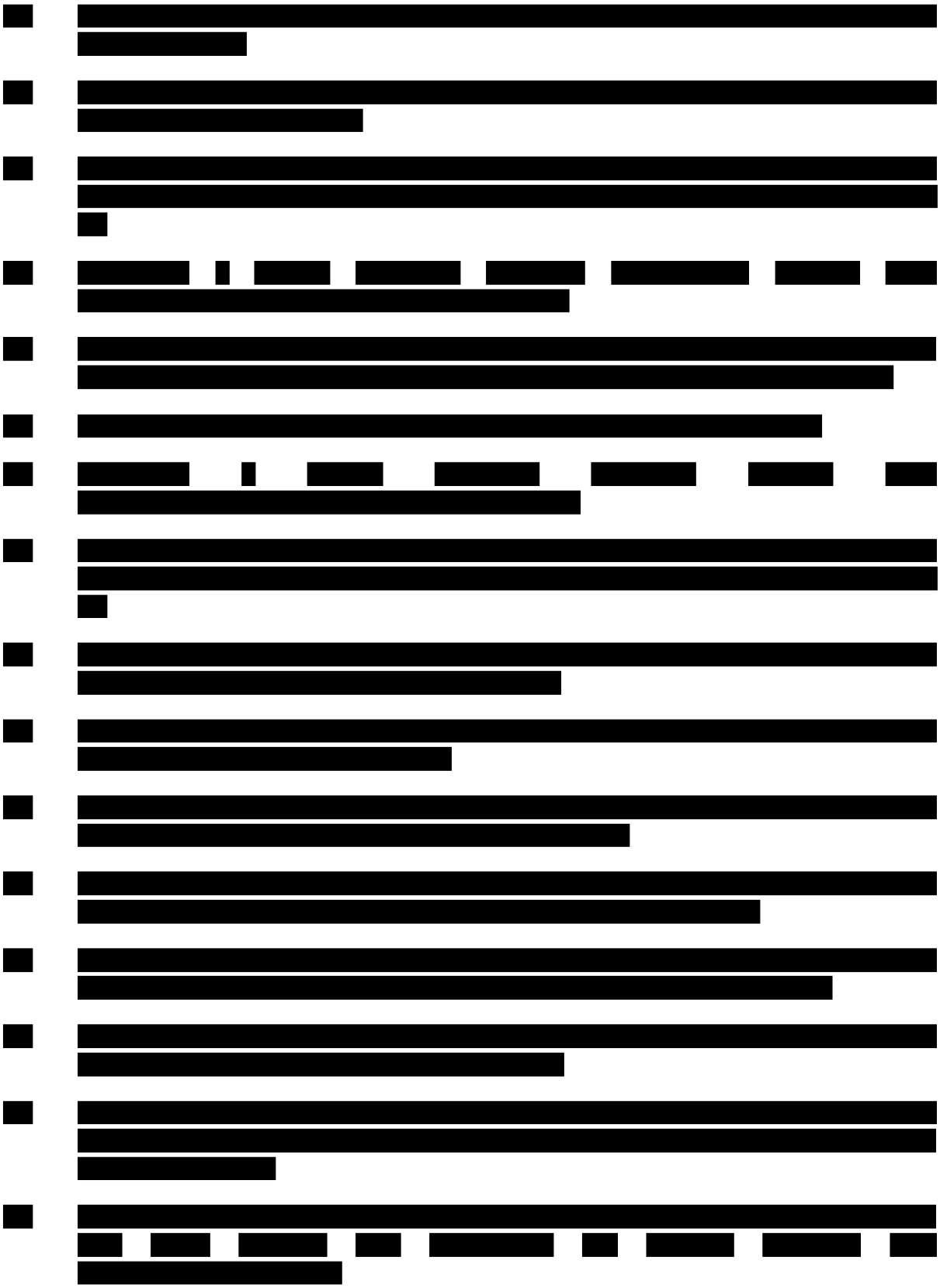
2.4 Nonclinical overview

[redacted]

2.4 Nonclinical overview

[redacted]

2.4 Nonclinical overview



2.4 Nonclinical overview

[redacted]

2.4 Nonclinical overview

[redacted]