2.5 Clinical Overview

Redacted under sections 41 and 43 of the FOI Act

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

2.5.1 PRODUCT DEVELOPMENT RATIONAL

2.5.1.1 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)	

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

2.5.1.2 INFORMATION ABOUT THE CONDITION

Mexiletine is indicated for the treatment of ventricular arrhythmias, which is considered as life-threatening by the physician [3].

Ventricular arrhythmias (VAs), including ventricular tachycardia (VT) and ventricular fibrillation (VF), are life-threatening complications of acute myocardial infarction (MI) [4]. The reported incidence of VF varies from 2.1 % to 12.4 %, depending on the population and duration of observation [5-19], and that of VT ranges from 1 % to 9.9 % [16, 20-22]. The incidence of both VF and VT in the same population has been reported to be 1.9 % to 10.2 %; however, these data are the result of a small number of studies because most reports detail the incidence of VT or VF but not both.

Ventricular fibrillation is the most common cause of death in the early phase of myocardial infarction [23]. In some cases it is preceded by other forms of ventricular arrhythmia but in others it occurs unexpectedly, without any warning.

2.5.1.3 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. The posology of the proposed products is in accordance with the withdrawn Mexitil product:

- 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 daily dose is between 600-800 mg in divided doses; optimal doses range from 300-1200 mg daily in divided doses.

Capsules should be swallowed whole with ample liquid, preferably with the patient in an upright position. It is advisable to take mexiletine after food.

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.

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

Table II Currently licensed Mexiletine products

Country and PL Number	Product Name	Dosage form	Strength (expressed as HCl)	Indications and Posology
France	Mexiletine APHP 200 mg, gélule	Capsules	200 mg	Myotonic dystrophy and non-dystrophic myotonia or channelopathy/ Starting dose: 1 capsule/day Maintenance dose: 1-3 capsules/day
EU (EU/1/18/1325/001–004)	Namuscla 167 mg hard capsules	Capsules	167 mg	Symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders/ Starting dose: 1 capsule/day After 1-week treatment: 2 capsules/day After a second-week treatment: 3 capsules/day Maintenance dose: 167-500 mg/day
Hungary (OGYI-T-3696/01-02)	Ritalmex 200 kapszula	Capsules	200 mg	Elimination of ventricular arrhythmias and prevention of life-threatening ventricular arrhythmias (excluding post-infarction patients)/ Saturation dose: 400-600 mg 2 hours after the first dose: 200 mg/6 hours Maintenance dose: 3×200 mg/day If necessary: 1200 mg/day
US (NDC 0597-(0066-68)-01)	Mexitil	Capsules	150 mg, 200 mg, 250 mg	Treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia/ Starting dose: 200 mg/8 hours Dose adjustment in 50 or 100 mg increments
Canada	Teva-Mexiletine	Capsules	100 mg, 200 mg	Treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia/ Starting dose: 200 mg/3 times daily Maximum dose: 1200 mg/day Titration: in steps of 100 mg/3 times daily

2.5.1.4 CLINICAL DEVELOPMENT PROGRAMME

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.

[redacted]

[redacted]

[redacted]

2.5.1.5 SEARCH STRATEGY

This Clinical Overview examines the current state of published scientific knowledge available on the clinical 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 Clinical 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 treatment of ventricular arrhythmias. 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]

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

2.5.2.1 PHARMACOKINETIC STUDY ([redacted])

In order to support the application, the applicant performed a single-arm pharmacokinetic study, in order to obtain pharmacokinetic data and actually investigate the in vivo pharmacokinetic characteristics of the test product Mexiletine 200 mg capsules, comparing them to available literature data from the public domain. This clinical trial in conjunction with the comparative dissolution profiles

presented in modules 2.7 and 3.2.P.2 serve as bridging data between the proposed product and other mexiletine products, including the historical EU reference product Mexitil.

The title of the study was:

An Open Label, Single Dose, Single-Treatment, Single-Period, Bioavailability Study of Mexiletine 200 mg Capsules of [redacted] *in Normal, Healthy, Adult, Human Subjects Under Fed Conditions.*

[redacted]

The purpose of the study was to determine the pharmacokinetic profile of the Test Product, Mexiletine 200 mg, Capsules in normal, healthy, adult, human subjects under fed conditions and to monitor the safety and tolerability of a single oral dose of the investigational medicinal product.

It was an open label, single-treatment, single-period, single dose study in 14 healthy, adult, human subjects under fed conditions. The number of subjects has been selected in order to have at least 12 evaluable patients at the end of the trial. Study has been conducted under fed conditions, according to the posology recommendations of Mexitil and other similar products (see discussion in section 2.5.2.4: Influence Of Food On Exposure)

A chiral bioanalytical assay was used to measure mexiletine in plasma, due to the fact that literature data suggest that the two enantiomers exhibit different pharmacokinetics. [redacted] the R/S AUC ratio was 2.94 ± 0.48 and the renal clearance of the R-enantiomer was significantly higher ($p<0.02$) than that of the S-enantiomer [26]. This approach has also been recommended during the scientific advice with the MHRA [25]. Therefore, the pharmacokinetic parameters of R- and S-Mexiletine as well as total mexiletine are reported in this section.

The following figures and tables summarize the pharmacokinetic parameters of the Test product. The pharmacokinetic parameters were calculated for R-Mexiletine and S-Mexiletine and total Mexiletine in plasma.

Table III: Pharmacokinetic data for total, R- and S-mexiletine [redacted]*)*

Pharmacokinetic parameter	Arithmetic Means (± SD)		
	Total Mexiletine	**R-Mexiletine**	**S-Mexiletine**
$AUC_{(0-72)}$	6717.393 ± 2002.877	3648.136 ± 1117.070	2994.020 ± 950.723
C_{max}	443.610 ± 79.336	248.409 ± 45.424	195.968 ± 35.150
K_{el} (λ_z)	0.078 ± 0.017	0.077 ± 0.016	0.070 ± 0.015
$t_{½}$	9.385 ± 2.292	9.410 ± 1.987	10.301 ± 2.291
*T_{max}	3.665 (1.670-8.000)	3.500 (1.670 - 8.000)	3.665 (1.670 - 8.000)

**Median (Min, Max)*

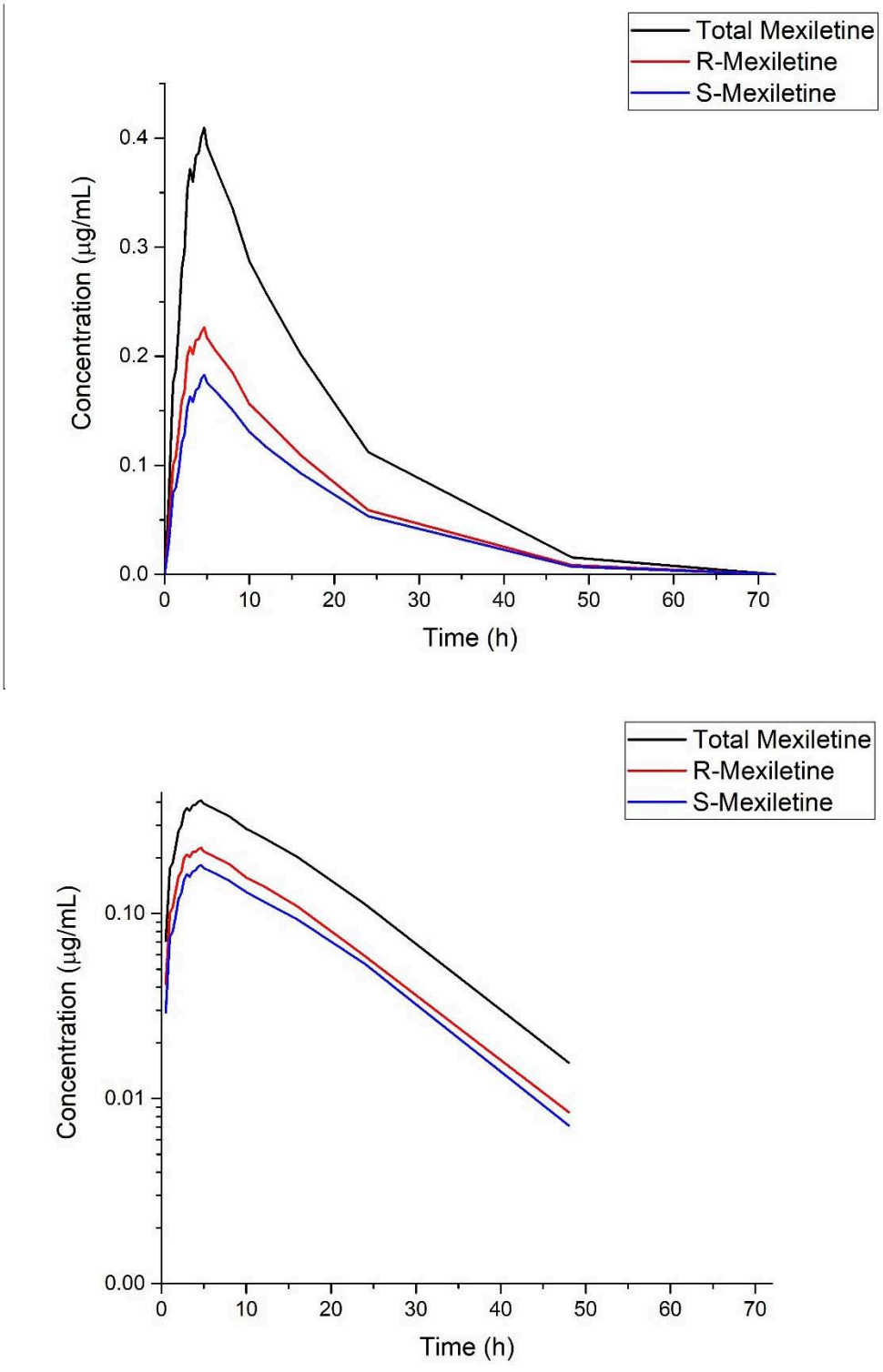


Figure 2: Concentration-time profiles for total, R- and S- mexiletine in the normal (top) and the logarithmic (bottom) scale

The results of the pharmacokinetic study indicate that the two enantiomers exhibit similar pharmacokinetics. The R-enantiomer exhibited higher AUC and C_{max} values. The ratio of the R/S enantiomers for the AUC and C_{max} values was approximately 55/45. Mexiletine is administered as racemic mixture of equal proportions. The literature data provide conflicting information, with some studies indicate similar and other different pharmacokinetics between the R- and the S- enantiomers (see section 2.5.3.1: Pharmacokinetics).

2.5.2.1.1 Comparison of the PK profile of the proposed product with literature data

The applicant used the pharmacokinetic data derived from the study [redacted] in order to compare them with the literature studies available on the public domain. The findings of these comparisons are presented in the following sections.

2.5.2.1.1.1 Comparisons with studies reporting plasma concentrations of total Mexiletine

Table XX in Appendix (Page 63) includes the pharmacokinetic data obtained from the public domain. C_{max} and AUC values were adjusted to the 200 mg dose, if needed. In total 23 studies were used in this analysis with doses ranging from 50 mg to 600 mg. The linearity of mexiletine's pharmacokinetics allows for such adjustment (see section 2.5.3.1.4: Linearity). Concentration time profiles for all available literature studies are provided in Figure 17 in Appendix.

The results of comparison of the pharmacokinetic parameters with the results obtained from study [redacted]7 are presented in Table IV below.

Table IV Comparison of pharmacokinetic data for total mexiletine between data from the public domain and study [redacted]7

	AUC_t (ng h/ml)		C_{max} (ng/ml)		T_{max} (h)	
	Mean	**Range**	**Mean**	**Range**	**Median**	**Range**
Literature	6004.3	3848-12910	532.8	325-1240	2.00	1.13-4.68
[redacted]	6717.4	4695-8720	443.6	329-591	3.67	1.67-8.00

In cases where literature studies provided plasma concentration – time profiles, the graphs were digitized [redacted] and dose-adjusted to the 200 mg dose, if needed. As a next step and with the intention to perform a direct curve comparison between the pharmacokinetic profile of the test product and literature data, a naïve pooled pharmacokinetic analysis was performed. All concentration-time data were pooled for the following time windows: 0–0.5, 0.5–1, 1-1.5, 1.5–2, 2–3, 3–4, 4–6, 6–8, 8–12, 12–16, 16-24, 24-36 and 36-48 h post-dose. The 25th percentile (Q1), 50th percentile (median), 75th percentile (Q3) of drug concentrations were calculated within each time window. Mean data and outliers were also included in the analysis. On top of this graph the plasma concentration-time profile of the test product was plotted (Figure 3).

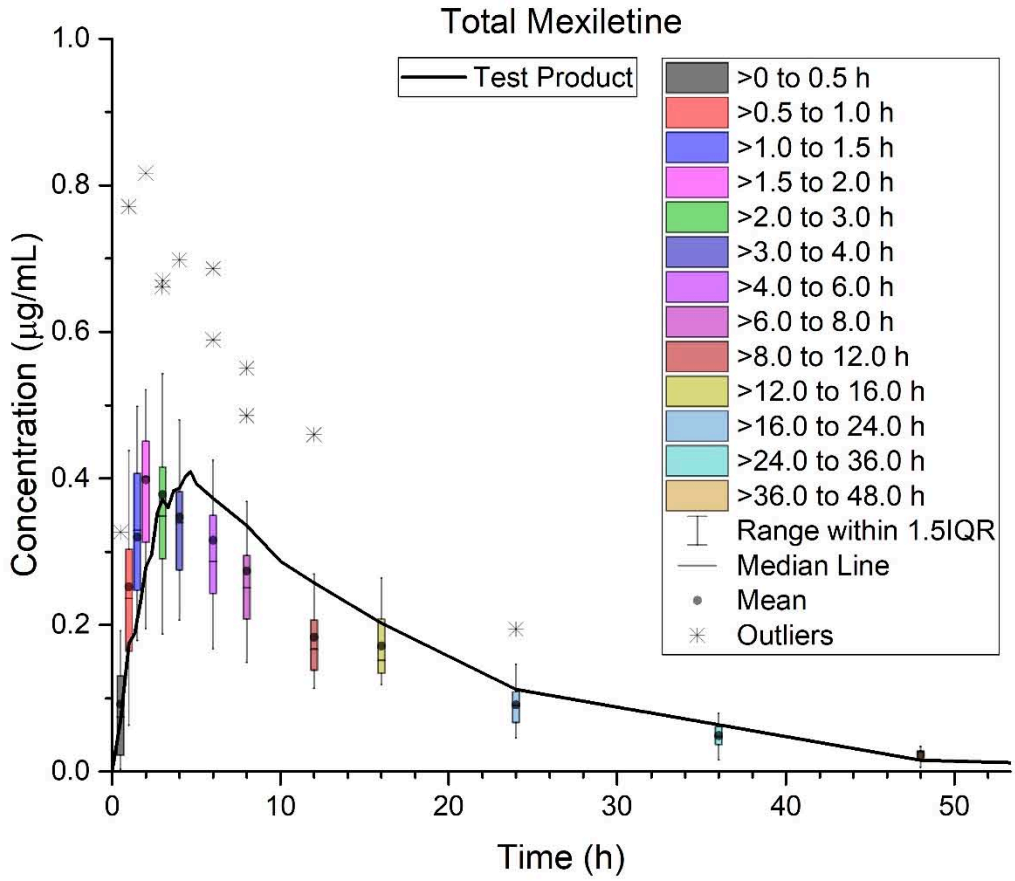


Figure 3 Concentration-time profiles of total mexiletine derived from literature data (box plots) and the test product (line plot)

The comparison of the pharmacokinetic parameters of total mexiletine with the pharmacokinetic parameters reported in literature (Table IV) indicate the AUC and C_{max} of the proposed product are within the range of literature data. C_{max} values were somewhat lower and the T_{max} was longer, suggesting a slower absorption rate. This is also evident in the direct curve comparison presented in Figure 3.

The reason for this difference is that the pharmacokinetic study [redacted] was performed under fed conditions, while all literature studies have been conducted under fasting conditions. A slightly delayed absorption is therefore anticipated. In a similar manner, the AUC was slightly higher. However, all PK parameter lie within the range of literature values and are also close with PK data from commercially available mexiletine products (see sections 2.5.2.1.2 and 2.5.2.1.3).

The observed delay in absorption is expected and results from a slower gastric emptying rate and/or increased gastric pH due to food ingestion. Delayed drug absorption caused by food does not necessarily mean that less of the drug is absorbed, but that the time for a drug to reach its peak blood level after a single dose is lengthened. Incidences whereby food delays drug absorption but does not affect the total amount of drug absorbed, are generally not clinically significant for most drugs. However, as seen in Section 2.5.2.1.2, all pharmacokinetic parameters of the proposed product are comparable with those reported for commercial available products.

2.5.2.1.1.2 *Comparison with studies reporting plasma concentrations of R- and S- Mexiletine*

Table XXI and Table XXII in Appendix (Page 68) includes the pharmacokinetic data obtained from the public domain for R- and S-mexiletine, respectively. C_{max} and AUC values were adjusted to the 200 mg dose, if needed. In total, 5 studies were retrieved, which included pharmacokinetic data for the two enantiomers. Mexiletine doses ranged from 200 mg to 300 mg. Concentration time profiles for all available literature studies are provided in Figure 18 in Appendix.

The results of comparison of the pharmacokinetic parameters with the results obtained from study [redacted] are presented in Table V and Table VII below.

Table V Comparison of pharmacokinetic data for R-mexiletine between data from the public domain and study [redacted]

	AUC_t (ng h/ml)		C_{max} (ng/ml)		T_{max} (h)	
	Mean	**Range**	**Mean**	**Range**	**Median**	**Range**
Literature	1937.5	1360-2800	203.5	190-217	2.1	2.1-2.1
[redacted]	3648.1	2531-4765	248.4	177-331	3.5	1.67-8.00

Table VI Comparison of pharmacokinetic data for S- mexiletine between data from the public domain and study [redacted]

	AUC_t (ng h/ml)		C_{max} (ng/ml)		T_{max} (h)	
	Mean	**Range**	**Mean**	**Range**	**Median**	**Range**
Literature	2058.3	1493-2600	176.3	157-196	2.3	2.3-2.3
[redacted]	2994.0	2043-3975	195.97	152-263	3.67	1.67-8.0

In a similar manner as with total mexiletine, the plasma concentration – time profiles were digitized and dose-adjusted to the 200 mg dose, if needed. All concentration-time data were pooled for the following time windows: 0–0.5, 0.5–1, 1-1.5, 1.5–2, 2–3, 3–4, 4–6, 6–8, 8–12, 12–16, 16-24, 24-36 and 36-48 h post-dose. The 25th percentile (Q1), 50th percentile (median), 75th percentile (Q3) of drug concentrations were calculated within each time window. Mean data and outliers were also included in the analysis. On top of this graph the plasma concentration-time profile of the test product was plotted (Figure 4 and Figure 5).

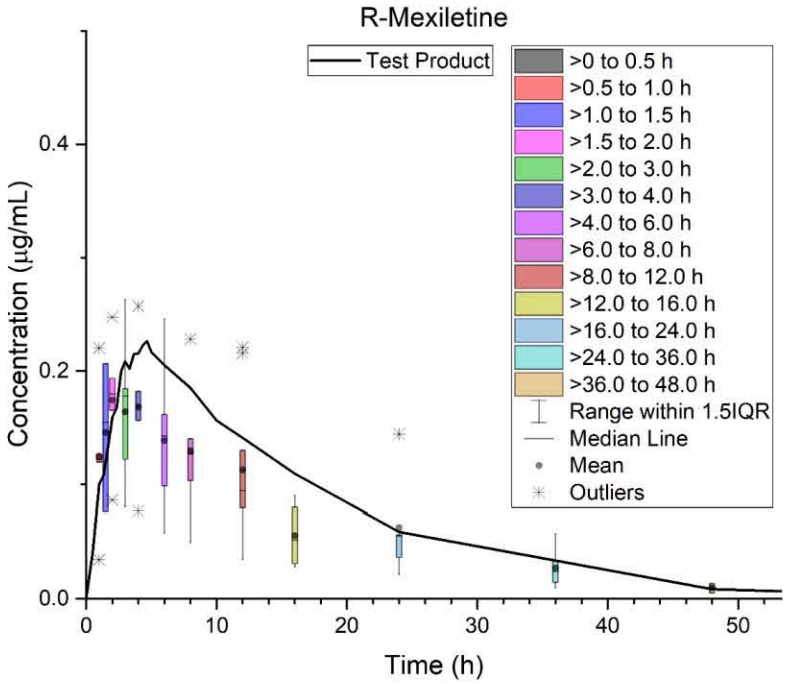


Figure 4 Concentration-time profiles of R-mexiletine derived from literature data (box plots) the test product (line plot)

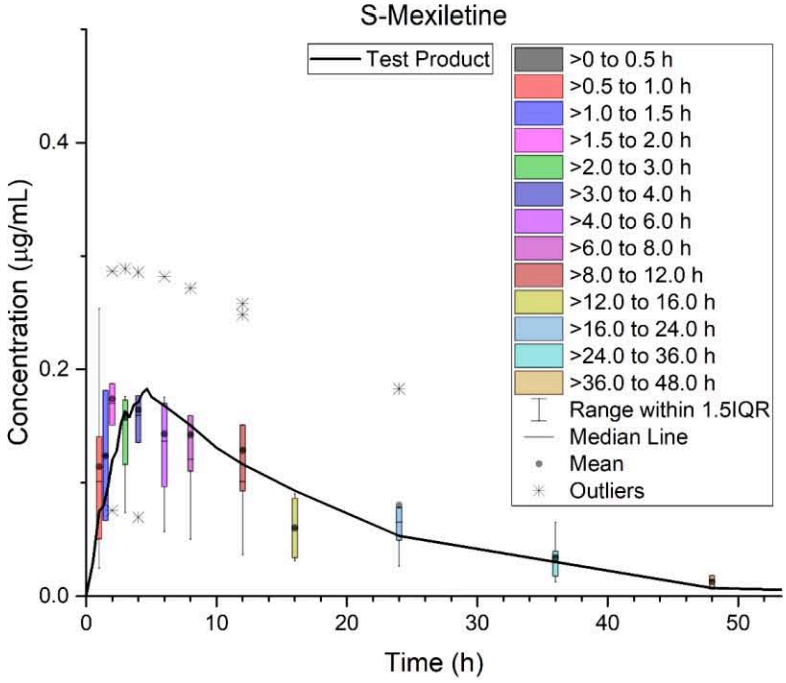


Figure 5 Concentration-time profiles of S-mexiletine derived from literature data (box plots) the test product (line plot)

Similarly with total mexiletine, the pharmacokinetic parameters of mexiletine enantiomers of the proposed product are comparable with literature data. The tabulated data and the direct curve comparison indicate a slightly slower and more extensive absorption for the proposed product. Both AUC and C_{max} values are higher than the average values reported to literature. The limited number of literature studies reporting R- and S- concentrations of mexiletine may have affected this comparison. Out of the five studies, only one exhibited markedly higher concentration than the test product [28].

2.5.2.1.2 Comparison of the PK profile of the proposed product with commercially available products

There are two Public Assessment Reports on the public domain (US and Canada), which include pharmacokinetic data for mexiletine products. Table VII presents the available pharmacokinetic data from commercially available mexiletine products. A comparison between the pharmacokinetic data of the test product and the dose-adjusted data under fed conditions is presented in Table VIII. Concentration time profiles for all available literature studies are provided in Figure 19 in Appendix.

Table VII Pharmacokinetic data of Mexiletine after oral administration of Mexiletine capsules (proposed product and other commercially available products)

Ref.	Product	Dose	Conditions	C_{max} (ng/ml)	AUC_t (ng h/ml)	T_{max} (hours)
[29]	Mexiletine Teva (T)	200	Fasting	342	4203	3.17
	Mexiletine Teva (T)	200	Fed	332	4311	4.1
	Mexitil Boehringer (R)	200	Fasting	310	3909	3.13
	Mexitil Boehringer (R)	200	Fed	297	3769	4.8
[30]	Mexiletine Danbury (T)	250	Fasting	498.5	5774.63	3
	Mexitil Boehringer (R)	250	Fasting	475.27	5603.46	2.77
	Mexiletine Danbury (T)	250	Fed	552.96	7287.24	2.65
	Mexiletine Danbury (T)	250	Fed	485.16	7013.88	4
	Mexitil Boehringer (R)	250	Fed	491.83	6840.18	3.29

Table VIII Comparison of pharmacokinetic data under fed conditions between commercially available mexiletine products and test product.

	AUC_t (ng h/ml)		C_{max} (ng/ml)		T_{max} (h)	
	Mean	Range	Mean	Range	Median	Range
PARs	4998.61	3769-5829	370.6	297-442	4.00	2.65-4.8
[redacted]	6717.39	4715-8740	443.6	329-591	3.67	1.67-8.00

As seen in Table VIII, all pharmacokinetic parameters of the proposed product (for total mexiletine) are comparable with those reported in the Public Assessment Reports of commercially available products. The difference in the Tmax values is now diminished, since the studies reported in Table VIII have been conducted under fed conditions. The average values reported in PARs are significantly affected by the low values of the TEVA PAR, which are on the low end of literature data (see also Table IV).

Figure 6 presents a direct curve comparison between the dose-adjusted concentration time profile of the Danbury product and the proposed formulation. The Danbury product also contains a reference product arm. Both studies have been conducted under fed conditions.

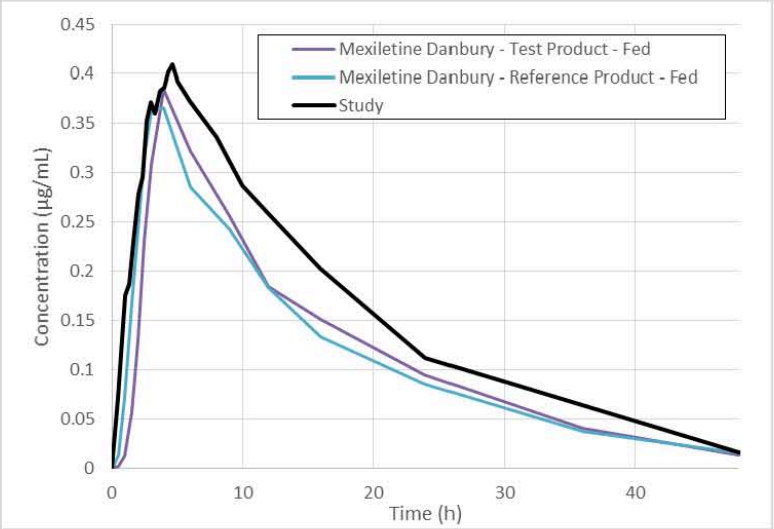


Figure 6: Concentration-time profiles of total mexiletine between data provided in the Danbury assessment report and proposed product.

Evidently, the study performed by the applicant proved that the bioavailability of the proposed products is comparable to those of immediate release mexiletine products (products used in the literature and commercially available products) being within the range and approaching the mean.

2.5.2.1.3 Bioequivalence studies from the Public Domain

Two bioequivalence studies have been retrieved from the public domain, both being successful. Mexiletine-Teva (200 mg capsules) was bioequivalent to the reference product Mexitil® 200 mg capsules of Boehringer Ingelheim Ltd. Bioequivalence was concluded in both studies under fasting or fed conditions, as reported in Table IX.

Table IX Pharmacokinetic parameters for mexiletine products [29].
Top row: Geometric means. Bottom row: Arithmetic Means ± C.V.

Parameters	Teva-Mexiletine (1 × 200 mg)		Mexitil ® (1 × 200 mg)		Percentage of Mexitil®	
	Fasting	Fed	Fasting	Fed	Fasting	Fed
AUC_t (ng h/mL)	4064 4203 ± 27	4137 4311 ± 29	3715 3909 ± 35	3669 3769 ± 24	109	113
AUC_{inf} (ng h/mL)	5115 5299 ± 28	4807 4961 ± 26	4722 4982 ± 34	4263 4372 ± 23	108	113
C_{max} (ng/mL)	337 342 ± 16	326 332 ± 19	305 310 ± 16	292 297 ± 18	110	112
T_{max} (h)	3.17 ± 0.65	4.1 ± 1.1	3.13 ± 0.64	4.8 ± 2.5	-	-
$T_{1/2}$ (h)	9.31 ± 2.53	9.2 ± 2.1	9.92 ± 3.29	8.6 ± 1.5	-	-

Bioequivalence was also concluded between Mexiletine of Danbury and Mexiletine of Boehringer Ingelheim, after administration of 250 mg of Mexiletine (capsules) in 24 subjects under fasting conditions and in 17 subjects under fed conditions [30]. Both studies indicate that mexiletine exhibits low intrasubject variability and the risk of bioinequivalence between mexiletine products is rather low.

2.5.2.2 DOSAGE FORM/STRENGTH PROPORTIONALITY

The proposed product is available at the strengths of 50 mg, 100 mg and 200 mg and the recommended dose is presented in Section 2.5.4.3.

The qualitative and quantitative composition of Mexiletine 50 mg, 100 mg and 200 mg Capsules is presented in Table X.

Table X Qualitative and quantitative composition of Mexiletine capsules

Ingredient	Function	Strength (label claim)					
		50 mg		100 mg		200 mg	
		Quantity per unit (mg)	%	Quantity per unit (mg)	%	Quantity per unit (mg)	%
Fill Formulation							
Mexiletine Hydrochloride	Active substance	50.0	62.5	100.0	62.5	200.0	62.5
Maize Starch	Binder/Diluent	28.8	36.0	57.6	36.0	115.2	36.0
Colloidal Silicon Dioxide	Glidant	0.8	1.0	1.6	1.0	3.2	1.0
Magnesium Stearate	Lubricant	0.4	0.5	0.8	0.5	1.6	0.5
Purified Water	Granulation liquid	8.75		17.5		35.0	
Fill Weight (cap, mg)		80.0	100	160.0	100	320.0	100
Capsule Size		4		3		1	

A biowaiver for the additional strengths (100 mg and 50 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 **, 2010):

- 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 are 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 (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
- appropriate in vitro dissolution data confirm the adequacy of waiving additional in vivo bioequivalence testing (data presented in Appendix 2-Dissolution profiles report- of 32P2-Drug development and module 2.7.1)
- Mexiletine has linear pharmacokinetics, as presented in Section 2.5.3.1.4 of the present document.

Since all the above mentioned requirements are met, a biowaiver can be applied for Mexiletine 50 mg and 100 mg capsules.

[redacted]

2.5.2.4 INFLUENCE OF FOOD ON EXPOSURE

Food does not affect the rate or extent of absorption of mexiletine. Therefore, mexiletine can be taken with or without food.

Several clinical studies have been conducted under either in fed or in fasted conditions. According to the SPC of Mexitil capsules of Boehringer Ingelheim Limited (PA 7/1/3), mexiletine should be taken after food consumption. This is also supported by the literature [31, 32] for preventing of gastrointestinal adverse effects. The SPC of TEVA-Mexiletine 100 mg and 200 mg Capsules states that Mexiletine should be taken with ample liquid, food and/or an antacid [29].

Mexiletine is recommended to be administered with food in order to reduce the incidence of adverse effects [33, 34] and therefore [redacted] was conducted in fed conditions. It is well known that food can affect both the rate and extent of drug absorption from the gastrointestinal tract. The delayed absorption or decreased rate of absorption usually results from a slower gastric emptying rate and/or increased gastric pH resulting from the ingestion of food. Pharmacokinetically, this is manifested as a decreased C_{max} and a corresponding longer t_{max} and/or lag time (t_{lag}) [35]. In fact, the slow rate of gastric emptying delays the onset of absorption, which usually occurs in the proximal region of the small intestine [36]. Thus, for a conventional formulation such as mexiletine, delayed absorption due to food consumption suggests that the rate limiting step in the absorption process is the delivery of the drug from the stomach to the small intestine [37]. However, this should be regarded as a clinically insignificant finding. Mexiletine is typically used in long-term treatment and at the steady state extent and not rate of absorption are critical for the plasma concentrations.

2.5.2.5 INFLUENCE OF METHOD OF ADMINISTRATION

The proposed products are intended to be administered as capsules only.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1 PHARMACOKINETICS

Mexiletine is administered as a racemic mixture of equal parts of the R-(–)- and S-(+)-enantiomers. Mexiletine undergoes stereoselective disposition in humans [26] and the enantiomers possess different antiarrhythmic potency [38].

The disposition of mexiletine is well established, both in healthy subjects and patients with different disease states, after both intravenous and oral administration. The pharmacokinetics of mexiletine after intramuscular injection were no different from those after intravenous administration except for

prolonged elimination of the hydroxymethyl metabolite. However, intramuscular administration has been employed rarely in clinical practice.

Overall, the pharmacokinetic parameters of mexiletine are summarized in table below (Table XI), as describe in the [redacted]

Table XI Mexiletine pharmacokinetics [39-45]

Parameter	Range
Bioavailability	80 - 88 %
First pass	< 10 %
T_{max}	1 – 4 h
Protein binding	60 – 75 %
Total V_d	5 – 12 L/kg
Cl_{tot}	6.5 - 10.3 ml/
K_e	0.016 - 0.058 h^{-1}
B $t_{1/2}$	6 – 12 h
Renal elimination	0.5 % (basic urine)
	50 % (acidic urine)

[redacted] reported the complete bioavailability of mexiletine administered by intramuscular injection in doses of 50 mg, 100 mg and 400 mg and the kinetics were linear with dose.

2.5.3.1.1 Absorption

Mexiletine is administered as a racemic mixture of equal parts of the R (-) and S (+) enantiomers. The absorption of mexiletine enantiomers is not stereoselective in humans [46]. Neither the absorption rate constants (K_a), C_{max} or time to C_{max} (t_{max}) differed significantly between mexiletine enantiomers. However, [redacted] reported a significantly higher C_{max} for R (–) mexiletine, when mexiletine was administered in 12 healthy subjects. The authors reported that the overall disposition of the mexiletine enantiomers is non-stereoselective and additionally a marked influence of serum pH on mexiletine serum free fraction was observed [47].

With single doses from 100 to 600 mg orally in 12 healthy volunteers there was a linear dose plasma concentration relationship with no dose-related change in the rate of total clearance (ranging from 40.4 to 57.0 L/h) or volume of distribution (ranging from 580 to 707 L) [48]. Doses of 400 and 600 mg produced peak plasma concentrations, after about 2 hours, in the therapeutic range of 0.75 to 2.0 mg/L.

The bioavailability of mexiletine after oral administration in healthy volunteers is 80 – 88 % [39, 41, 43-45, 49].

The pharmacokinetics of mexiletine are unchanged in patients with arrhythmias relative to those reported in healthy volunteers. Thus, in 10 patients with premature ventricular contractions (PVCs) a peak plasma concentration of 0.44 mg/L was achieved 2.6 hours after a single oral dose of 150 mg; with repeat dosing (150 mg tid) for 5 days steady-state was achieved after 4 to 5 days with no accumulation. However, in patients with acute myocardial infarction (AMI) there is delayed absorption of mexiletine [50].

2.5.3.1.2 Distribution

After intravenous injection plasma mexiletine concentrations fall rapidly as a result of extensive uptake and distribution; only about 1 % of the total amount of drug in the body is in the plasma after distribution [51]. A 3-compartment model best describes the disposition kinetics of mexiletine, with fast and slow distribution phases and a much slower elimination phase. The extensive tissue uptake is reflected in the large but very variable volume of distribution. Volumes of distribution of 663 ± 238 L in healthy volunteers and 755 ± 517 L in patients with myocardial infarction have been also reported. It is independent of oral dose, and mean values ranged from 580 to 707 L at doses from 100 to 600 mg [48]. As a result of uptake into erythrocytes, which appear to act as a deep compartment for mexiletine, blood concentrations of mexiletine have been reported to be about 12 % higher than serum concentrations [52].

Serum protein binding of mexiletine has been reported to be about 70 %. McErlane et al demonstrated stereoselective binding of mexiletine to serum proteins in vitro, with about 30 % greater binding of the R (-) enantiomer than the S (+) enantiomer. [redacted] hat the plasma concentration of the R (-) enantiomer is consistently lower than that of the S (+) enantiomer in healthy volunteers after oral administration of the conventional 200 mg capsule of racemic mexiletine [53].

2.5.3.1.3 Metabolism and Excretion

Mexiletine is extensively metabolised in humans by oxidative and reductive processes and by conjugation, to form the metabolites parahydroxy-mexiletine (PHM), hydroxyl-methylmexiletine (HMM) and their corresponding alcohols [54]. Only about 8 to 15 % of an administered dose is eliminated in urine in unchanged form [49]. Although these metabolites do not have a significant antiarrhythmic activity, patients with low metabolism capacity (slow metabolizers) may present high plasma concentrations of unchanged mexiletine in situations of administration for therapeutical doses of the drug.

Its elimination and plasma concentration is affected by urinary pH [55].

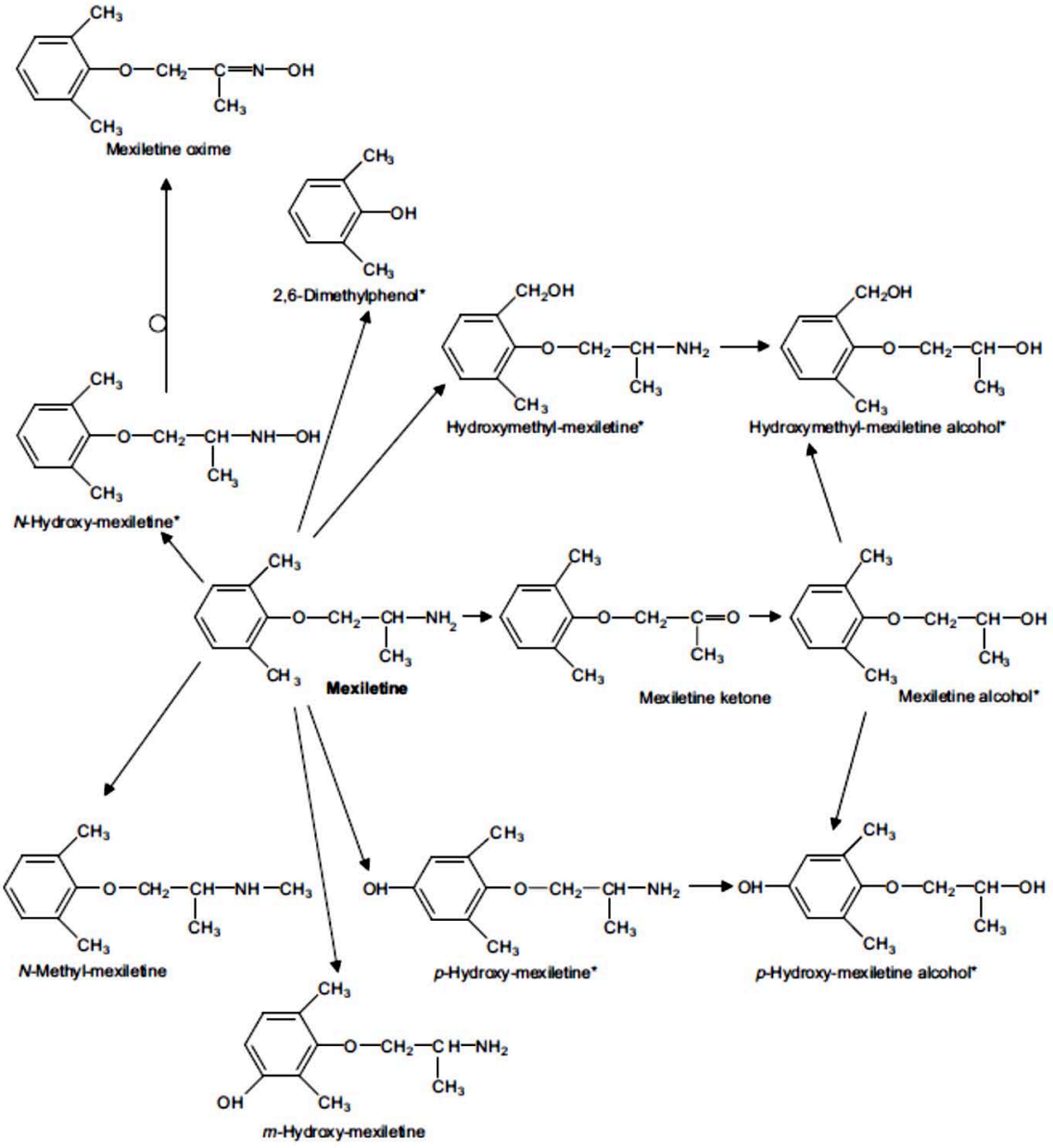


Figure 7 Metabolic pathways of mexiletine in humans [50]

Although mexiletine is administered as racemic form, few studies have reported the stereoselective kinetic disposition of mexiletine, probably due to the low plasma concentrations of the enantiomers. A study by [redacted] [38] showed that the antiarrhythmic activity of the enantiomer R (-) mexiletine administered to dogs is higher than that of the S (+) enantiomer.

[redacted] [26] reported higher plasma concentrations of S (+) mexiletine than of the corresponding R (-) enantiomer in healthy subjects treated with a single dose of racemic mexiletine. Although the serum concentrations of S (+) mexiletine were always higher than those of its antipode,

the difference in the concentrations of the two enantiomers was never large enough to compensate for the amount of S (+) mexiletine that was not conjugated. This suggests that part of the S (+) mexiletine that is not conjugated is metabolized via another pathway.

In a study on the same population, [redacted] [46] reported a larger volume of distribution and a prolongation of the terminal elimination half-life for the S (+) enantiomer. [redacted] [53] demonstrated a stereoselectivity on the in vitro serum protein binding of mexiletine in healthy volunteers. Free drug of R (-) enantiomer was approximately 30 % less than that of the corresponding S (+).

The pharmacokinetic parameters derived from the plasma concentrations of mexiletine enantiomers were investigated by [redacted] [56]. They demonstrated that kinetic disposition of mexiletine exhibits stereo-selectivity and that aliphatic hydroxylation is favoured for R (-) mexiletine in Chagasic women with ventricular arrhythmias.

Table XII: Pharmacokinetic parameters of mexiletine enantiomers after an oral dose of 200 mg t.i.d. of (±) mexiletine hydrochloride. Values are reported as mean (CI 95 %) [56]

Parameter	S (+) Mexiletine	R (-) Mexiletine
C_{max} (ng/ml)	452.01 (384.22-519.81)	428.36 (373.42-483.31)
T_{max} (h)	2.00 (1.23-2.77)	1.71 (0.81-2.61)
K_a (h^{-1})	1.71 (0.99-2.42)	1.83 (0.88-2.78)
A (h^{-1})	1.62 (0.24-3.49)	0.66 (0.51-0.82)
$T_{1/2\beta}$ (h)	9.24 (6.25-12.22)	8.70 (6.78-10.62)
$T_{1/2\gamma}$ (h)	28.93 (23.76-34.09)	32.47 (14.05-50.89)
AUC^{SS}_{0-8} (µg.h.ml^{-1})	2.55 (1.97-3.13)	2.34 (1.84-2.85)
Cl/F (ml.ml^{-1}.kg^{-1})	10.46 (7.18-13.74)	11.27 (7.77-14.77)
Vd/F (l.kg^{-1})	8.59 (4.60-12.58)	8.56 (4.99-12.12)
$AUC_{S(+)}/AUC_{R(-)}$	1.08 (1.02-1.15)	

Renal clearance of mexiletine in healthy volunteers after oral doses from 100 to 600 mg was 40.4 to 57.0 L/h, and was independent of dose [48]. However, this is highly dependent on urinary pH, being much greater in an acidic pH [43, 55]. In 5 healthy volunteers after mexiletine 3 mg/kg intravenously there was a predicted increase in steady-state plasma concentration of mexiletine of 39 % with alkaline urine (pH 8.0) versus acidic urine (pH 5.0) [43].

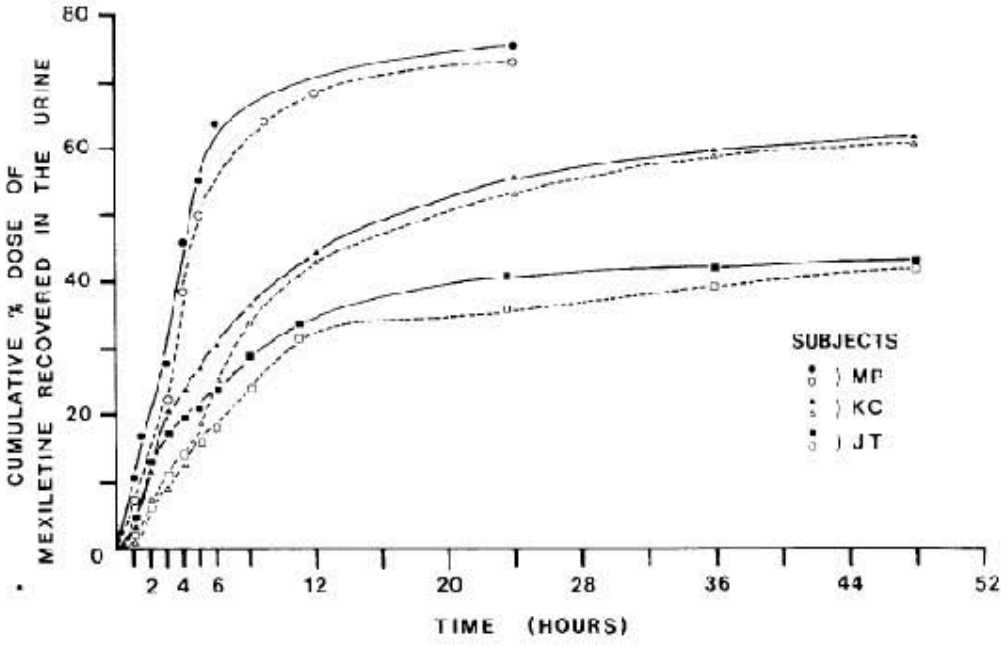


Figure 8 Cumulative excretion of unchanged Mexiletine in the urine after oral dose of Mexitil capsules (solid line) and hospital-modified Mexiletine capsules (dotted line) to 3 subjects (MP [-▫- & -•-], KC [-Δ- & - ▪ -} and JT [-▫- & -▫-]). [57]

2.5.3.1.4 Linearity

Literature data demonstrate that that during refractory ventricular arrhythmias, the mean plasma concentrations and AUC of mexiletine are directly proportional to the administered dose. [redacted] evaluated the pharmacokinetics of 100, 200, 300, 400 and 600 mg mexiletine after oral administration in healthy volunteers. As seen in Table XIII and Figure 9, as the dose of mexiletine was increased there was a progressive and linear increase in the maximum plasma concentration and in AUC [48].

Table XIII Pharmacokinetic parameters for mexiletine after oral administration [48]

Pharmacokinetic parameters	Dose (mg)				
	100	200	300	400	600
C_{max} (ng/ml)	177	381	560	885	1223
C_{max} (ng/ml) (Dose adjusted to 200 mg)	354.0	381.0	373.3	442.5	407.7
AUC_{0-t} (ng h/ml)	2511	5094	6870	11373	16438
AUC_{0-t} (ng h/ml) (Dose adjusted to 200 mg)	5022.0	5094.0	4580.0	5686.5	5479.3

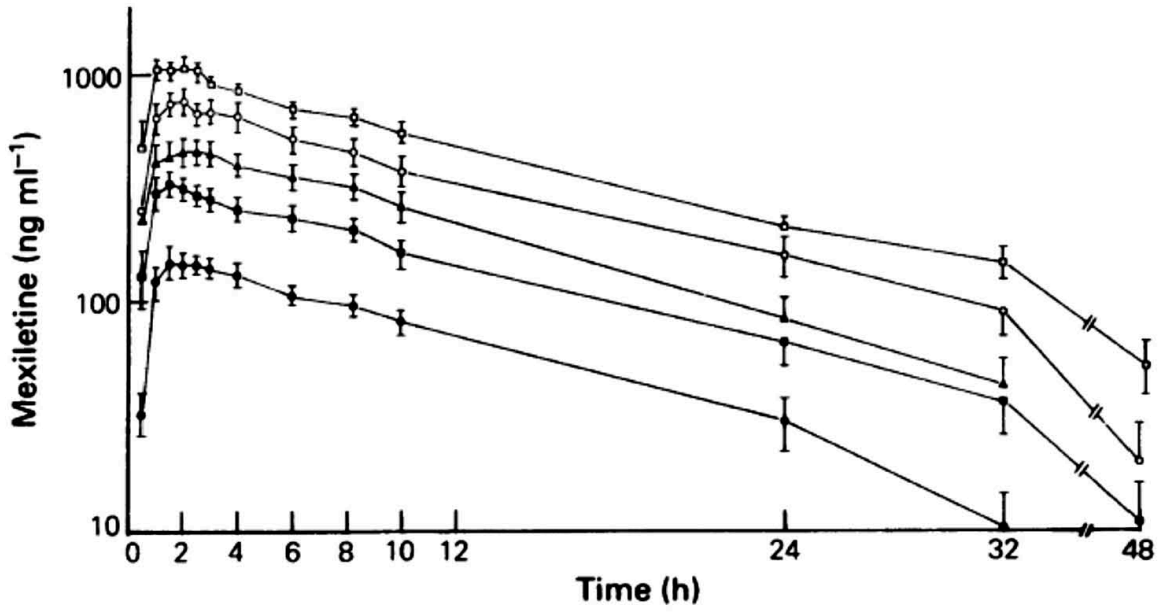


Figure 9 Plasma concentrations of mexiletine (mean ± s.e. mean ng/ml) during the 48 h period following oral doses of 100 mg (●), 200 mg (▪), 300 mg (▲), 400 mg (○) and 600 mg (□) mexiletine in each of 12 healthy volunteers [48]

In another study, mexiletine in doses of 50, 100 and 400 mg was administered by intramuscular injection to healthy subjects and the resulting plasma concentrations were compared with those after 100 mg given intravenously. The results demonstrated that the bioavailability of mexiletine given by this route is complete and the kinetics are linear with dose [41].

The study of [redacted] confirms also the findings [redacted] regarding the linearity of mexiletine. 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 to healthy volunteers, resulting in a dose dependent increase of C_{max} and AUC (Figure 10). There were significant correlations between dosage (mg/kg) and C_{max} ($r=0.87$, $p<0.01$) or AUC ($r=0.91$, $p<0.01$) [58].

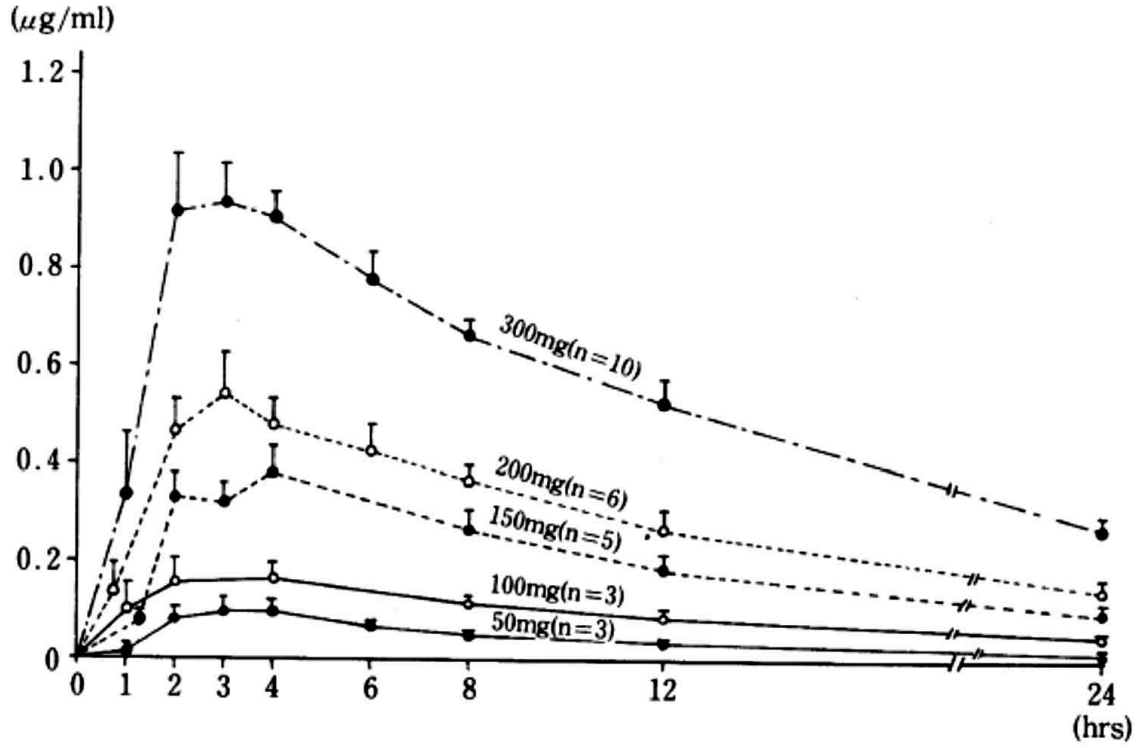


Figure 10 Plasma concentrations of Mexiletine versus time following oral administration [58]

2.5.3.1.5 Pharmacokinetic studies in special population

Since different pharmacokinetic parameters have been observed in special populations, such as patients with severe hepatic disease or patients with creatinine clearance of less than 10 ml/min, individual dose titration is recommended.

2.5.3.1.5.1 Genetic polymorphism

Genetically determined patterns of drug metabolism can influence the individuals' response to drug therapy as a result of highly variable plasma concentrations of the parent compound or its metabolites.

One of the most widely studied polymorphisms in drug oxidation is the metabolism of the antihypertensive agent debrisoquine to its 4-hydroxy metabolite. In fact, in the late 1970s, it was reported that the alicyclic 4-hydroxylation of debrisoquine was bimodally distributed [59]. On the basis of an 8-hour urinary excretion profile following a single oral dose of debrisoquine 10 mg, a metabolic ratio (defined as the percentage dose excreted as debrisoquine divided by the percentage dose excreted as 4-hydroxydebrisoquine) discriminated between 2 distinct phenotypes [59]. Individuals with a ratio greater than 12.6 were defined as poor metabolisers (PMs) whereas a value less than this antimode reflected an ability to extensively metabolise (EMs) the probe drug [60, 61]. Further studies indicated that the biochemical basis of this genetically determined drug polymorphism was related to the activity of a specific cytochrome P450 (CYP) isozyme, namely CYP2D6 [62-64].

The disposition of over 30 other pharmacological agents, including mexiletine, cosegregates with the debrisoquine 4-hydroxylase polymorphism. In fact, it was demonstrated that the formation of

hydroxymethyl-mexiletine, p-hydroxy-mexiletine andm-hydroxy-mexiletine is genetically determined and cosegregates with CYP2D6 activity [65, 66]. In vitro studies performed with human liver microsomes suggested that the formation of hydroxymethyl-mexiletine and p-hydroxy-mexiletine was predominantly catalysed by CYP2D6 [66-68]. The formations of these 2 metabolites of mexiletine were competitively inhibited by quinidine, several CYP-2D6 substrates and an antiserum containing antiliver/kidney microsome antibodies type I (anti-LKM1) directed against CYP2D6. These results were confirmed by other in vivo studies [65, 68-70].

[redacted] investigated the role of debrisoquine polymorphism and the effects of low dose quinidine on the disposition of mexiletine in 14 healthy volunteers: 10 EMs and 4 PMs. Each volunteers received a single dose of mexiletine hydrochloride 200 mg orally on 2 occasions 1 week apart, one dose alone and the other dose under steady state conditions for quinidine 50 mg 4 times daily. The disposition of mexiletine was different between EMs and PMs after administration of mexiletine alone. Mean plasma concentrations of mexiletine were higher in those with the PM phenotype compared with the EM group. The $t_{1/2\beta}$ was longer in the PM group [median and range: 12.6h (8.9- 14.8h)] than in the EM group (mean ± SD: 8.9 ± 1.1h). The systemic clearance (CL), CLNR and partial metabolic clearance (CLPM) of mexiletine to hydroxymethyl-mexiletine, p-hydroxy-mexiletine or m-hydroxy-mexiletine were all decreased in the PM group compared with the EM group [65]. Moreover, quinidine treatment selectively altered mexiletine disposition in Ems [65]. In these individuals, the addition of quinidine increased the mean drug plasma concentrations and $t_{1/2\beta}$ of mexiletine. CYP2D6 inhibition by quinidine also produced a decrease in the CL, CL_{NR} and CL_{PM} of mexiletine to hydroxymethyl-mexiletine, p-hydroxymexiletine and m-hydroxy-mexiletine. The administration of quinidine altered the pharmacokinetics of mexiletine to an extent such that differences were no longer observed between the EM and PM groups. In PMs, quinidine did not alter mexiletine plasma concentrations, nor did it significantly change any of the derived pharmacokinetic parameters. These results were confirmed by another study which showed a decreased urinary excretion of hydroxymethyl-mexiletine and p-hydroxy-mexiletine in EMs after quinidine administration [69]. Thus, formation of hydroxymethyl-mexiletine, phydroxy- mexiletine and m-hydroxy-mexiletine is largely mediated by CYP2D6 and is under genetic control.

Other CYP isozymes also contribute to the formation of hydroxymethyl-mexiletine, p-hydroxymexiletine and m-hydroxy-mexiletine. In fact, formation of these metabolites was impaired but not prevented in PMs and partially abolished by quinidine co-administration in Ems [65]. Moreover, in vitro studies using human liver microsomes provided biochemical evidence that CYP2D6 is the predominant, but not sole, enzyme responsible for the formation of hydroxymethyl-mexiletine and phydroxy- mexiletine [66, 67]. The formation of these 2 metabolites was strongly reduced, but not completely abolished, by several CYP2D6 substrates, by quinidine and by an antibody direct against CYP2D6.

The selective induction by cigarette smoking (a well-known inducer of CYP1A2) [71] of formation of hydroxymethyl-mexiletine, but not p-hydroxymexiletine, also suggests that different CYP isozymes besides CYP2D6 are responsible, at least in part, for the formation of these metabolites [72]. [redacted] [73] reported that mexiletine p- and methyl-hydroxylations are catalyzed partially by CYP1A2 in human liver microsomes and by recombinant human cytochromes. The contribution of CYP1A2 to these 2 hydroxylation pathways of mexiletine is relatively low.

Although CYP2D6 is clearly involved in the formation of hydroxymethyl-mexiletine, p-hydroxymexiletine and m-hydroxy-mexiletine, the N-oxidation of mexiletine is not mediated by this

CYP isozyme. In fact, the CLPM of mexiletine to N-hydroxy- mexiletine was not different between PMs and EMs with mexiletine alone and not altered in EMs during quinidine co-administration [65]. Evidence has accumulated to suggest the role of CYP1A2 in the metabolism of mexiletine and formation of N-hydroxy-mexiletine in humans. First, studies have shown that cigarette smoking alters the kinetics of mexiletine in humans and increases the formation rate of a N-glucuronide metabolite (characterised as N-hydroxy-mexiletine glucuronide) [72, 74]. Secondly, in vitro studies performed with microsomes from yeast cells expressing high levels of specific CYP activity showed that the formation rate of N-hydroxy-mexiletine by CYP1A2 was more than 50 times greater than that observed with microsomes expressing low CYP activity [75]. Moreover, the formation rate of N-hydroxy-mexiletine measured in human liver microsomes correlated well with 7-ethoxyresorufin deethylase activity, and furafylline (40 µmol/L), a potent and selective inhibitor of CYP1A2 [76], decreased the formation rate of N-hydroxy-mexiletine by 60 % [75].

Since in vitro studies with human liver microsomes have suggested that the oxidative conversion of mexiletine to its metabolites is catalysed by CYP2D6 and is significantly impaired in microsomes with the CYP2D6*10/*10 genotype, the influence CYP2D6*10 allele on mexiletine pharmacokinetics was examined by [redacted] The authors demonstrated that carriers of the CYP2D6*10 allele showed a decreased clearance of mexiletine. Subjects with CYP2D6*5/*10 showed significantly ($p<0.05$) increased plasma levels of mexiletine and homozygotes for CYP2D6*10 also showed an increase, although to a lesser extent [77].

2.5.3.1.5.2 *Age*

[redacted]. compared the kinetics of an oral dose of mexiletine 100 mg between 2 groups: a young group (19 to 37 years) and an elderly group (65 to 79 years). No age-related differences in lag-time were noted but the K_a was significantly higher in the younger group. In this group, the C_{max} and T_{max} tended to be higher and shorter, respectively. Neither the $t_{1/2\beta}$ nor CL/F were significantly different between the 2 groups [78].

[redacted] obtained a linear decrease of apparent CL/F with age [79]. The decrease in mexiletine clearance in elderly patients was explained by factors similar to those affecting resting metabolic rate [79]. Indeed, resting metabolic rate in elderly men (mean age 75 years) is about 20 % lower than in young men (mean age 21 years) [80].

2.5.3.1.5.3 *Body Weight*

Body weight has been reported to affect significantly both clearance and volume of distribution [45, 81].

2.5.3.1.5.4 *Hepatic impairment*

Cirrhosis of the liver markedly alters the pharmacokinetics of mexiletine [82, 83]. The steady state serum concentration of mexiletine is significantly higher in patients with cirrhosis of the liver compared with patients without liver disease [83].

Following administration of a single intravenous dose of mexiletine hydrochloride 200 mg to patients with cirrhosis or healthy controls, the CL and elimination rate constant were significantly lower in patients with cirrhosis compared with the control group [82]. Indeed, the mean $t_{1/2\beta}$ of mexiletine in patients with cirrhosis was 2.9 times that found in the control group. The rate of distribution, V_d at steady state (V_{ss}) and V_d of the central compartment (V_c) remained unchanged.

2.5.3.1.5.5 *Renal impairment*

The effects of renal failure on the pharmacokinetics of mexiletine were evaluated by [redacted] [84]. Mexiletine 50 mg was administered orally 3 times daily for 10 days to 15 patients with chronic renal failure [creatinine clearance (CL_{CR}) lower than 1.8 L/h] and to 9 control individuals. When CL_{CR} was above 0.6 L/h, the pharmacokinetic parameters of mexiletine were not significantly modified by chronic renal failure. However, the plasma concentrations at steady state and $t_{1/2\beta}$ of mexiletine were increased when CL_{CR} was below 0.6 L/h [84].

Other studies have reported no correlation between the degree of renal failure and CL/F or $t_{1/2\beta}$ of mexiletine in a group of patients with CL_{CR} in the ranges of 0 to 4.13 L/h, 0.12 to 2.4 L/h or 0.3 to 0.9 L/h [85]. No differences in plasma concentrations were noted between control patients with normal renal function and patients with renal insufficiency (CL_{CR} < 4.5 L/h) receiving mexiletine 200 mg 3 times daily [83].

There was no significant removal of mexiletine from plasma during haemodialysis, haemofiltration, peritoneal dialysis or plasmapheresis in 20 dialysis patients [86]. In 5 individuals requiring long term haemodialysis, no differences were observed between AUCs during dialysis and during the day on which the patients did not receive dialysis [85]. Similarly, 2 case reports found no significant changes in the rate of removal of mexiletine following peritoneal dialysis [87, 88].

2.5.3.1.5.6 *Cigarette smoking*

The effects of cigarette smoking, a CYP1A2 inducer [71], on the pharmacokinetics of a single oral dose of mexiletine 200 mg were studied in 2 groups of young volunteers: 6 smokers and 8 non-smokers [72]. Cigarette smoking had no effects on the absorption and distribution of mexiletine. However, the $t_{1/2\beta}$ was significantly shorter in the smoking group (7.2 ± 1.8 h vs 11.1 ± 3.4 h). The effects of cigarette smoking on the CL of mexiletine were also apparent, with the mean value in non-smokers 25 % less than that found in the smoker groups.

Measurement of the urinary excretion of 3 metabolites of mexiletine showed that the formation rates of hydroxymethyl-mexiletine and mexiletine N-glucuronide conjugate were significantly higher in smokers compared with non-smokers. However, there were no differences in the formation rate of p-hydroxy-mexiletine. In contrast, [redacted] did not report an increase in formation rate of hydroxymethyl-mexiletine in smokers [68].

2.5.3.1.5.7 *Myocardial infarction*

The influence of acute myocardial infarction on the pharmacokinetics of mexiletine has been evaluated in several studies. [redacted] [89, 90] performed 2 studies to investigate the kinetics of mexiletine following single doses of the drug during the acute and recovery phases of myocardial infarction. In these studies, a 400 mg oral dose or 200 mg intravenous dose of mexiletine hydrochloride were administered to patients (oxycodone was co-administered to most patients). Both studies performed included 2 phases: the acute phase, within 24 hours of the onset of pain, and the recovery phase, 7 to 14 days following myocardial infarction. The C_{max} of mexiletine were significantly lower during the acute phase than the recovery phase following oral administration [90]. This was explained by the slower and delayed gastrointestinal absorption of mexiletine in the acute phase study. The T_{max} and absorption $t_{1/2}$ tended to be higher during the acute compared with recovery phase; however, there were no significant differences in these parameters because of the wide interindividual

variability, especially in the acute phase study. In addition, the extent of absorption remained unchanged.

Others have confirmed these changes in patients admitted to coronary care units early after the onset of myocardial infarction. [redacted]. [91] showed that 3 hours after the first dose of mexiletine (600 mg on arrival and 200 mg 2 hours later), mean concentrations of the drug were significantly lower in patients with myocardial infarction than in those without. [redacted] [89, 90] showed a prolongation of mexiletine $t_{1/2\beta}$ in the acute phase of myocardial infarction. This prolongation of $t_{1/2\beta}$ was explained by an increase in the V_{ss} and the V_d during the γ-phase (V_γ) of the drug. Following intravenous administration of mexiletine, the CL was similar in the acute and recovery phases, while V_{ss} and V_γ were significantly higher (about 30 %) in the acute phase. The increased V_{ss} and V_γ could also explain the lower plasma mexiletine concentrations found in the acute phase of myocardial infarction. The CL_R of mexiletine was not changed during the acute and recovery phases of myocardial infarction [89, 90].

2.5.3.1.5.8 *Cardiac failure*

[redacted] did not observed any significant prolongation of the $t_{1/2\beta}$ in 6 patients with clinical evidence of congestive heart failure [42].

[redacted] did not observed any difference in mexiletine concentrations in patients with congestive heart failure [83]. No significant effects of congestive heart failure on the V_β/F or CL/F of orally administered mexiletine was also found [45].

2.5.3.1.5.9 *Ventricular arrhythmias*

The pharmacokinetics of mexiletine are unchanged in patients with ventricular arrhythmias.

During refractory ventricular arrhythmias, the mean plasma concentrations and AUC of mexiletine were directly proportional to the administered dose, suggesting first order elimination kinetics as observed in healthy volunteers [92].

2.5.3.2 PHARMACODYNAMICS

2.5.3.2.1 Electrophysiology

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. The primary mechanism of action, as established in early experimental studies, involves blockade of the fast sodium channel resulting in reduction of the maximum velocity of phase 0 of the cardiac action potential. The emphasis in experimental studies with mexiletine has been to investigate the electrophysiological effects of antiarrhythmic drug combinations [51].

Additionally, in vitro and in vivo models suggest that mexiletine reduces muscle fibre excitability caused by common NDM (Non-Dystrophic Myotonias) mutations. In the past, the treatment was mainly symptomatic and addressed the problem of sarcolemma hyperexcitability. Between drugs with the ability to inhibit generation and propagation of action, potential through the block of voltage-gated sodium channels are effective in this respect. Mexiletine, a sodium channel blocker, targets the primary defect in sodium channelopathies (excessive activation of the sodium channel SCN4A channel protein) [93].

2.5.3.2.2 Cardiovascular Hemodynamic effects

Mexiletine, whether administered orally or intravenously, has no clinically significant effect on resting heart rate or blood pressure in healthy volunteers [94] or patients treated for ventricular arrhythmias [95]. Small increases in heart rate and blood pressure, possibly associated with the local anaesthetic properties of mexiletine, have been reported in some patients [96]. Mexiletine has no influence on peak heart rate or blood pressure during exercise in patients with ventricular arrhythmias and impaired left ventricular function [95, 96].

[redacted] reported no significant effect of mexiletine 50 or 100 mg as a bolus injection, nor of 350 to 500 mg by intravenous infusion, on any haemodynamic variable in 24 patients with ventricular ectopic beats [97]. Similarly, in patients with ventricular arrhythmias and ischaemic heart disease and/or congestive heart failure, orally or intravenously administered mexiletine had no effect on mean haemodynamic values [98].

There was no significant effect of intravenous mexiletine 150 mg or 2.75 mg/kg on systemic or pulmonary vascular resistance, stroke work index or cardiac index, and only a minor increase in mean pulmonary artery pressure, in patients with valvular heart disease but no heart failure [99].

2.5.3.2.3 Cardiac function

In a controlled study in 8 healthy volunteers single oral doses of mexiletine 200 mg or disopyramide 100 mg had no significant effect on cardiac function [94].

Patients with ventricular arrhythmias but without significant impairment of cardiac function were included in a 12-month study of the effects of 4 times daily oral administration of mexiletine 200 mg, disopyramide 100 mg and procainamide 600 mg on cardiac function assessed by M-mode echocardiography. The negative inotropic effects of mexiletine at rest were less than those of the alternative drugs after both 6 and 12 months.

Since the primary clinical indication for mexiletine is the treatment or prevention of ventricular arrhythmias, and many of these patients may have impaired cardiac function, the influence of this drug on cardiac haemodynamics in patients with reduced ejection fraction is of importance. Studies employing doppler echocardiography have reported little change in mean ejection fraction or other parameters of left ventricular function following therapeutic doses of mexiletine. Mexiletine produced no further deterioration of cardiac function in those relatively short term studies [100].

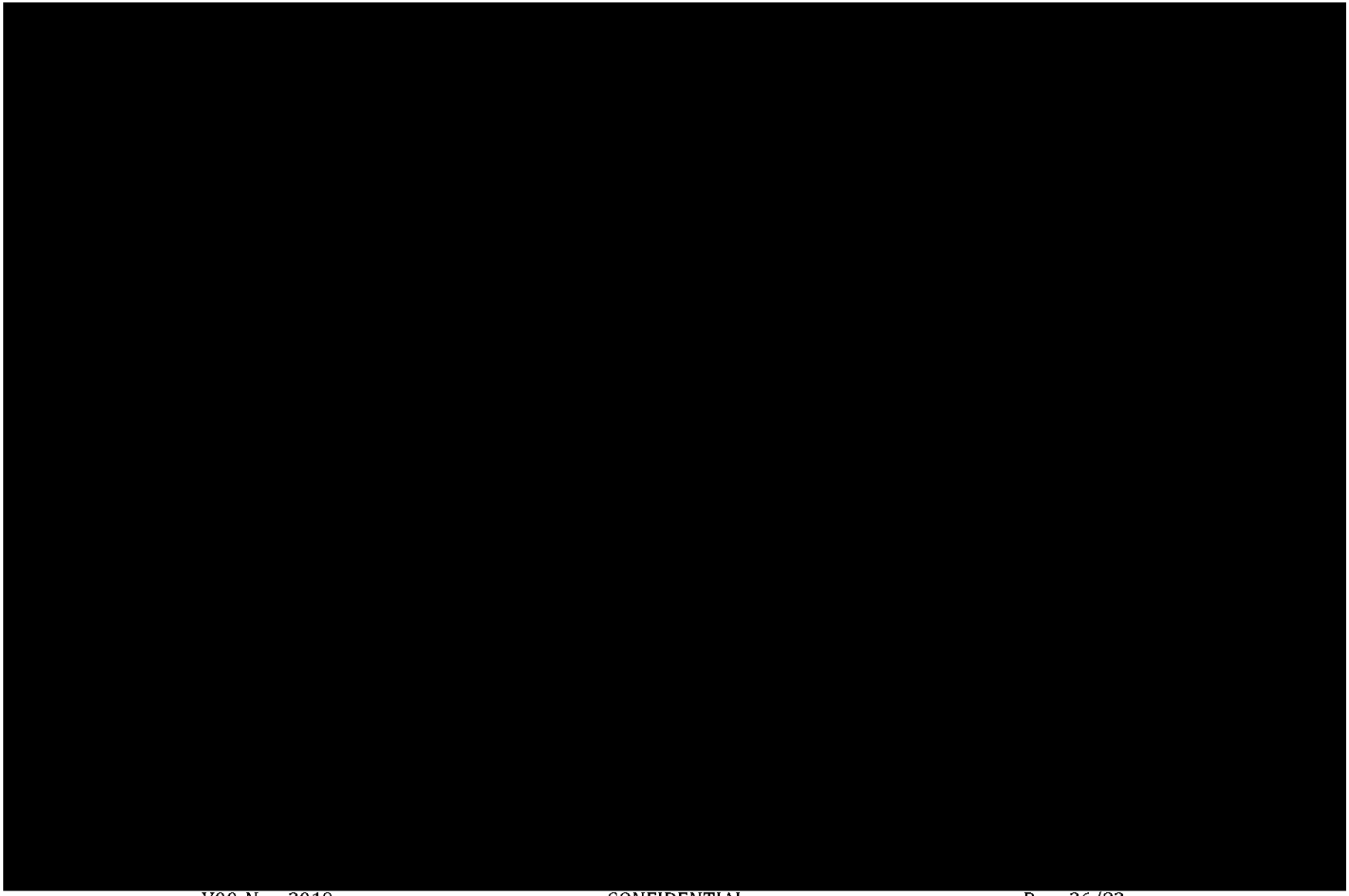
In the study reported by [redacted] all 14 patients evaluated had atherosclerotic heart disease and 7 had congestive heart failure. At a mean daily dosage of 621 mg mexiletine had no significant effect on resting or peak exercise left or right ventricular ejection fraction or wall motion score. Similarly, neither quinidine 1573 mg daily nor the combination of mexiletine and quinidine adversely affected ventricular function [96].

2.5.4 OVERVIEW OF EFFICACY

Literature data evaluating the efficacy of mexiletine in ventricular arrhythmias are summarised in Table XIV below.

2.5 Clinical overview

2.5 Clinical overview



2.5 Clinical overview

[redacted]

2.5.4.1 VENTRICULAR ARRHYTHMIAS

2.5.4.1.1 Comparative studies

2.5.4.1.1.1 *Comparisons to placebo*

[redacted] performed a double-blind study involving 165 patients in order to assess the efficacy of mexiletine on the prophylaxis of ventricular arrhythmias after acute myocardial infarction. Mexiletine or placebo (initial 600 mg oral dose followed by 200 mg at 2 hours and a further 200 mg at 4 hours) was given orally to patients on arrival in the coronary care unit and continuous electrocardiographic tape recordings were used to document arrhythmias (EKGs). Ventricular arrhythmias and R or T ventricular ectopic beats were significantly reduced in the mexiletine patients. When arrhythmias occurred in the mexiletine group, it was usually early in the study, at which time plasma drug levels were low [99]. Results are also presented in Figure 11.

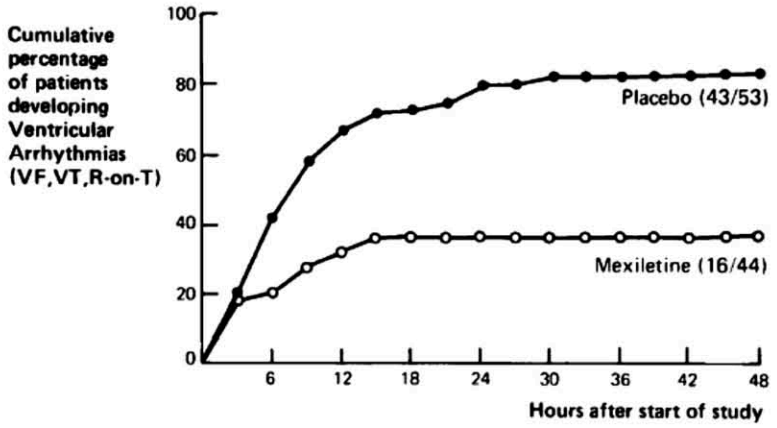


Figure 11 Cumulative incidence of serious ventricular arrhythmias in mexiletine and placebo patients related to time from start of study [99]

Mexiletine has been also studies in patients with drug-resistant ventricular tachycardia. In the study of Heger, Mexiletine therapy was administered to 15 patients with chronic and recurrent episodes of ventricular tachycardia or ventricular fibrillation. All patients were intolerant of or had arrhythmias resistant to conventional antiarrhythmic agents. At maximal dosages of mexiletine 2 patients had more than 90 % reduction in frequency of premature ventricular complexes, whereas 11 patients had less than 50 % reduction, as measured on 24 hour electrocardiographic recordings. Mexiletine was unsuccessful in preventing or abolishing ventricular tachycardia in 11 patients [92]. In another placebo-controlled study twelve patients who had a median of 294 such complexes/hour were admitted to the study. Eleven completed 4 weeks of trial with mexiletine and placebo with ambulatory electrocardiographic (Holter) recordings taken at the end of each treatment period. The doses given were designed to reduce the frequency of premature ventricular complexes by 50 % or more from the baseline value. Mexiletine significantly reduced the rate of premature ventricular complexes by comparison with placebo (-66 % versus 3 %, p=0.032). In addition, mexiletine reduced the median number/hour of ventricular couplets observed. After 4 weeks of therapy, 2, 2, 1 and 6 patients, respectively, were taking 100, 200, 300 and 400 mg of mexiletine every 6 hours. Mexiletine produced no significant change in baseline values including electrocardiographic intervals, blood pressure or heart rate [101].

Another double-blind, crossover study was designed by [redacted] in order to compare the safety and efficacy of mexiletine with that of placebo in reducing premature ventricular complexes (PVC) in ambulatory patients and to find out the dose which gives a good therapeutic response with a minimal incidence of side-effects. Twenty-six patients who had on average 427.9 PVCs/hour, were admitted to the study. The doses given were designed to reduce the frequency of PVCs by 50 % or more from the baseline value. Two out of the twenty-six patients stopped treatment because of major side-effects. In the remaining twenty-four patients the 3 weeks of treatment with mexiletine significantly reduced the rate of PVCs by comparison with placebo (-63·8 % versus +7·5 %). In the nineteen responders (per cent reduction of PVCs over 50 %) the dose of mexiletine was 600 mg daily (200 mg every 8 hours) (Figure 12). In the non-responders plasma levels of mexiletine proved to be in the therapeutic range, not in any way different from responders [102].

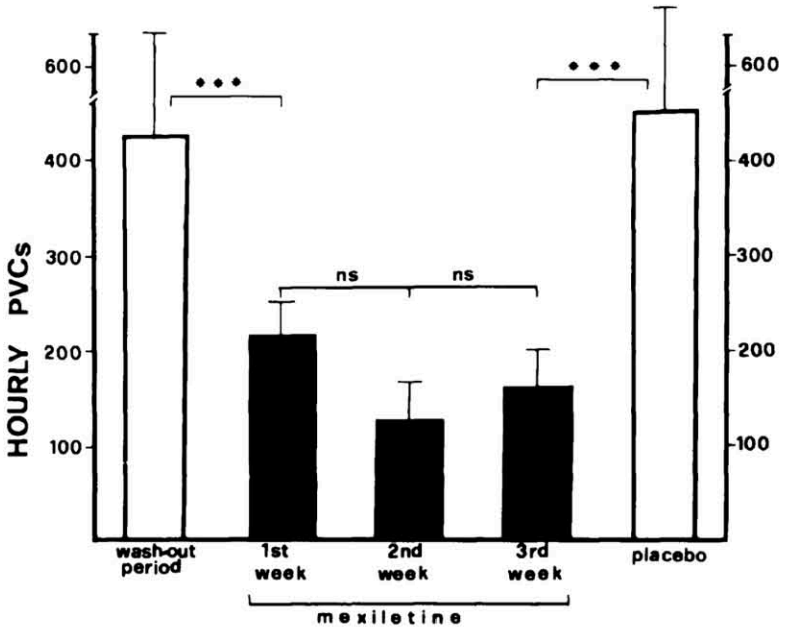


Figure 12 Effects on PVC reduction of treatment with mexiletine and placebo in the 24 patients who completed the study protocol. [102]

[redacted]) reported that sustained release mexiletine 360 mg twice daily was as effective in preventing the occurrence of arrhythmias in patients not having arrhythmias as baseline as it was in reducing the incidence of arrhythmias in those having pre-existing arrhythmias. 630 patients with recent documented myocardial infarction were enrolled in the study. The marked difference in occurrence of frequent or complex cardiac arrhythmia in mexiletine-treated patients compared with the placebo-treated patients was not accompanied by a reduced mortality rate. The percent of patients who died was 7.6 and 4.8% in the mexiletine and placebo groups, respectively; this difference was not statistically significant [103].

The antiarrhythmic effects of the sustained release form of mexiletine were evaluated in a double-blind placebo trial in 630 patients with recent documented myocardial infarction. The primary response variable was based on central reading of 24 hour ambulatory electrocardiographic recordings and was defined as the occurrence of 30 or more single premature ventricular complexes in any two consecutive 30 minute blocks or one or more runs of two or more premature ventricular complexes in the entire 24 hour electrocardiographic recording. Large differences, regarded as statistically

significant, between the mexiletine and placebo groups were noted in that end point at months 1 and 4, but only trends were observed at month 12. These differences were observed even though the serum mexiletine levels obtained in this study were generally lower than those observed in studies that have used the regular form of the drug [135].

[redacted] evaluated the effects of oral mexiletine on left ventricular (LV) ejection fraction (EF) and ventricular arrhythmias-and a possible relation between these effects, during 3 months of therapy in 29 patients with chronic ventricular premature complexes (VPCs). After an average titration period of 13 days, a mean daily mexiletine dose of 739 mg was maintained throughout the treatment. At the end of titration and after 3 months of treatment, patients with a baseline LVEF 140 % (group 2) responded with a median reduction of the hourly VPC rate by 90 and 81 %, respectively, compared with 79 and 72 % in those with a baseline LVEF >40 % (group 1). Couplets and runs of ventricular tachycardia were almost completely suppressed in nearly all patients. A single patient had a pro-arrhythmic increase in VPCs during treatment. Compared with baseline, there were no significant changes in resting or exercise LVEF after 1 or 3 months of treatment in either of the 2 groups of patients. Additionally, no correlation was found between treatment-induced changes in arrhythmia frequency and in resting EF and no symptoms of congestive heart failure developed [104].

The antiarrhythmic efficacy of mexiletine in acute myocardial infarction (AMI) was studied in 99 patients randomized to mexiletine or placebo treatment. The loading dose was 250 mg i.v. and 400 mg orally followed by 200 mg orally 2h later, and thereafter 200 mg t.i.d. up to 42 h. Arrhythmias occurring during 48 h were analysed from continuous electrocardiographic recording. AMI was verified in 35 of 50 mexiletine patients and in 38 of 49 placebo patients. The number of patients who had any event of accelerated idioventricular rhythm (AIVR; $P<0.05$), runs of ventricular premature beats (VPBs; $P<0.01$), ventricular tachycardia ($P<0.01$) and RonT beats ($P<0.05$) was smaller in the mexiletine group than in the placebo group [105].

In the study of [redacted], intravenous and oral mexiletine, compared to placebo, resulted in reduced frequency of atrial fibrillation, supraventricular tachycardia and ventricular extrasystoles in 240 high risk patients with acute myocardial infarction. However, ventricular tachycardia and primary ventricular fibrillation were not prevented [106].

[redacted] investigated the antiarrhythmic effect of oral mexiletine (200-250 mg every 8 h) in 344 patients at high risk after acute myocardial infarction in a double blind trial.

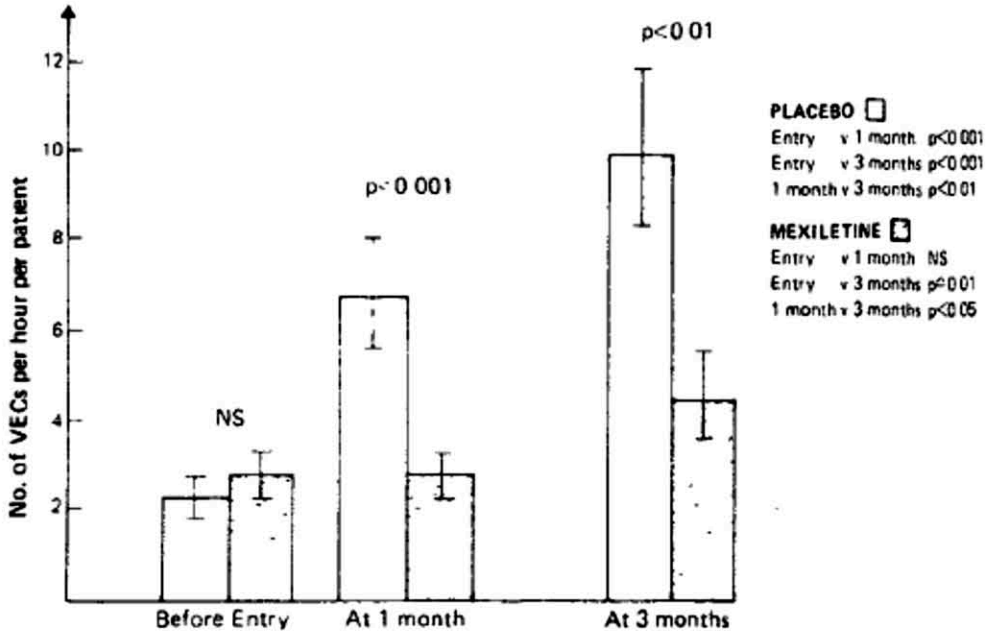


Figure 13 Average number of ventricular ectopic complexes (VECs) per patient-hour (normalised by log transformation) with standard errors and significant values [107]

It is evident (Figure 13) that with regard to arrhythmia-prevalence, mexiletine produced a highly significant reduction in the frequency of ventricular ectopic complexes [107].

2.5.4.1.1.2 *Comparisons to other drugs or Combined Therapy*

The first study that combined mexiletine with another antiarrhythmic agent, was the study of [redacted] In 4 patients studied, the combination of mexiletine and propranolol proved to be beneficial in severe ventricular arrhythmias when mexiletine alone has either failed or caused adverse effects. The treatment with mexiletine begun with a dose of 200 mg every eight hours and then mexiletine was reduced to the highest dose that failed to produce adverse effects and propranolol was added all four patients achieved either greater than 80 % suppression of ventricular premature depolarisations or absence of ventricular tachycardia, or both [108]. Beneficial effects were also demonstrated for the combination of mexiletine and propranolol in 14 patients with stable or reproducible ventricular extrasystoles of various aetiologies [109].

A combined mexiletine and amiodarone treatment was applied in nine cases with recurrent refractory ventricular tachycardia. During the first two days of treatment, mexiletine and amiodarone were perfused intravenously at a dose of 1,000 mg and 1,500 mg per 24 hours, respectively. Simultaneously amiodarone was also given orally at a dose of 600 mg per 24 hours. From the third day onwards, the intravenous administration was interrupted and both drugs were continued orally at a dose of 600 mg daily. The first three patients were very critically ill and had had at least five episodes of ventricular tachycardia per 24 hours during the last 10 days in the intensive care unit. The treatment resulted in total suppression of the tachycardic episodes within three days after initiation of therapy. In the remaining six cases, ventricular tachycardia was easily initiated by programmed electrical stimulation

of the heart. No arrhythmia could be elicited by repeated testing on the seventh day of treatment [110].

The antiarrhythmic efficacy of mexiletine was also evaluated by [redacted] in 44 patients with drug-resistant ventricular tachy-arrhythmias. In 33 of these patients, the efficacy of mexiletine was assessed on the basis of the results of programmed ventricular stimulation. Mexiletine did not alter the ventricular effective refractory period, the Q-Tc interval, or the methods of tachyarrhythmia induction and termination during programmed stimulation. The mean cycle length of ventricular tachycardia (VT) increased from 270 ± 49 to 313 ± 80 ms in 21 patients in whom VT remained inducible on mexiletine alone ($p < 0.002$). Overall, VT remained inducible with methods similar to control (no drugs) inductions in 25 patients receiving mexiletine alone or in combination with a type I agent. VT induction was prevented in only 8 patients, 3 on mexiletine alone and 5 receiving mexiletine combined with another drug. Mexiletine alone (in 2 patients) or with another agent (in 3 patients) suppressed clinical recurrence of VT in an additional 5 of 11 patients who did not undergo electrophysiologic study. These 13 patients were discharged on mexiletine alone (5 patients) or in combination with other drugs (8 patients), and remained arrhythmia- free over a mean follow-up period of 7.7 ± 4.1 months [111].

The efficacy of mexiletine as an adjunctive therapy to amiodarone in patients with an implantable defibrillator was examined in the cohort study of [redacted] 29 patients were treated with a median dose of 300 mg/day and there was a significant reduction in the incidence of ventricular tachycardia/fibrillation episodes (median 2 vs. 12 events, $p = 0.001$) and shocks (median 0 vs. 2 events, $p = 0.003$) in the first 3 months of treatment, but long-term efficacy was only observed among patients who continued amiodarone therapy [112].

Another study that recently examined the combined effects of mexiletine and amiodarone in this group of patients showed that adding mexiletine to amiodarone had no significant effect on QRS width, QTc interval and PR interval. A significant decrease in the number of total ICD shock and significant increase in appropriate antitachycardia pacing during follow up after initiating mexiletine was observed. Additionally, mexiletine therapy significantly reduced the amiodarone dose during the follow up [113].

The electrophysiologic effects and clinical efficacy of mexiletine used alone or in combination with class IA agents were studied in 35 patients with recurrent sustained ventricular tachycardia (VT) or ventricular fibrillation refractory to nonexperimental antiarrhythmic agents by [redacted]. At baseline before therapy, all patients had inducible VT by programmed stimulation (1 to 3 extrastimuli) and frequent (at least 30/hour) ventricular premature complexes (VPCs) during Holter monitoring. Mexiletine therapy was effective by programmed stimulation (VT no leer inducible or 15 or less beats) in 8 and ineffective in 27 patients. Twenty patients were discharged with mexiletine (14 of whom took an additional class IA agent). The discharge regimen was effective by programmed stimulation in 8 of these 20 patients. In 14 patients the discharge regimen was ineffective by programmed stimulation, but all patients had a marked reduction of ventricular ectopic activity (at least 83% reduction of VPCs and abolition of non-sustained VT). During the follow-up period of 18 ± 13 months (mean ± standard deviation), 4 patients had recurrences (3 with an ineffective regimen by programmed stimulation and 1 with an effective regimen by programmed stimulation). Arrhythmia-free survival rates at 12 and 24 months were 86 % and 77 %, as determined by the Kaplan-Meier method, in patients with an ineffective regimen by programmed stimulation, and 80 % and 80 % in patients with an effective regimen by programmed stimulation ($p = 0.979$ by log rank test) [114]. Another study that combined mexiletine with class IA antiarrhythmic drugs was this of Whitford et al that assessed 159 previously

drug-refractory patients with ventricular tachycardia (VT) during serial electrophysiologic studies and during long-term (5-year) clinical follow-up. Electrically-inducible ventricular tachycardia was suppressed by mexiletine alone in 23% of patients tested, and a combined antiarrhythmic drug regimen was effective in 29 % of the trials performed. Mexiletine was much more likely to be effective in patients presenting with non-sustained VT or ventricular fibrillation than in patients with sustained VT ($p < 0.005$). After 1 and 4 years of treatment, 18 % and 42 % of the patients treated with mexiletine alone had died suddenly or suffered recurrent symptomatic VT, compared to 11 % and 25 % of patients treated with the combined antiarrhythmic drug regimens (p = NS) [34].

The greater efficacy of mexiletine in comparison with lignocaine was demonstrated in the study of [redacted] Mexiletine was given as an initial bolus of 200 mg, followed by an infusion of 1 mg/min reduced to 0.5 mg/min after 1 hr and lignocaine was given as a bolus of 100 mg, followed by an infusion of 3 mg/min reduced to 2 mg/min after 1 hr in 24 patients who developed ventricular tachyarrhythmias within 48 hr of the onset of acute myocardial infarction. The frequency of "complex" ventricular tachyarrhythmias was significantly lower in the mexiletine-treated group [115].

The literature search revealed lots of studies comparing the efficacy of mexiletine to this of quinidine or the combination of both. Seventeen of the 21 patients had ischemic heart disease; five had episodes of ventricular fibrillation, six had recurrent, sustained ventricular tachycardia requiring cardioversion, and the remainder had episodic non-sustained ventricular tachycardia. As the dosage of mexiletine was gradually increased, only three patients' arrhythmias were controlled without limiting side effects. One patient continued to have episodic ventricular fibrillation during mexiletine therapy and was excluded from the remainder of the study. The other 17 patients had a partial antiarrhythmic response (the mean suppression of ventricular ectopic depolarizations [VEDs] was 62.5 + 25 %) and 10 continued to have ventricular tachycardia), but dose-related side effects limited therapy (at a mean dose of 950 + 202 mg/day). These 17 patients had not responded to or did not tolerate quinidine (mean dose of 1042 + 362 mg/day). With the maximum well-tolerated dosage of quinidine, the mean suppression of VEDs was 59.16 %. Eleven of 17 patients (64 %) continued to have ventricular tachycardia with quinidine, and therapy was limited by side effects (diarrhea) in 11. In the group of 17 patients, the addition of a previously well-tolerated dosage of quinidine (824 + 298 mg) to a well-tolerated but only partially effective dosage of mexiletine (800 + 239 mg) produced a significantly greater antiarrhythmic response. The mean suppression of VEDs during combination therapy increased to 85.9 + 26 %. Only one patient continued to have ventricular tachycardia, and limiting side effects occurred in only 12 % of the patients. Continuation of quinidine and withdrawal of mexiletine was associated with recurrence of complex ventricular arrhythmias and documented the need for combination treatment in nine patients. Electrocardiographic intervals were measured at baseline, during mexiletine therapy and during combination therapy. The coupling interval of the predominant ectopic beat prolonged ($p < 0.05$) during mexiletine treatment and further prolonged ($p < 0.05$) with the addition of quinidine. After withdrawal of mexiletine from the combination treatment in nine patients, the QTc interval significantly prolonged ($p < 0.05$). Thus, mexiletine limited the quinidine-induced increase in QTc interval. During 18 ±.2 months of follow-up, three patients have died, one with intractable congestive heart failure and two related to documented noncompliance to their medical regimen. The addition of quinidine, which prolongs repolarization of the action potential in vitro, enhanced the antiarrhythmic efficacy of mexiletine, which shortens the action potential duration in vitro [116]. The same additional effect was also noticed previously by the same group, concluding in enhanced antiarrhythmic efficacy of mexiletine [136]. Combination quinidine-mexiletine therapy suppressed also 80 % of ventricular premature complexes in 13 of 14 patients and suppressed 100 % of episodes of ventricular tachycardia

in 6 of 8 patients (mean quinidine dose 200 ± 70 mg; mean mexiletine dose 146 ± 24 mg every 8 h) [117].

Another study that compared mexiletine and quinidine in 26 ambulatory patients with chronic ventricular ectopy. Thirteen patients were treated with mexiletine and 13 with quinidine. The treatment groups were comparable in age and cardiac diagnoses, in frequency of untreated ventricular ectopy, in the presence of complex forms, and in previous drug failures. After two 24-hr ambulatory ECG recordings, the patients were treated according to a double-blind, dose-ranging protocol. Efficacy was defined as reduction in ventricular ectopic frequency by at least 70 % in a comparison of two 24-hr ambulatory ECG recordings after drug with the two pretreatment recordings. Suppression of ventricular ectopic frequency by at least 70 % was achieved in seven mexiletine-treated patients and eight quinidine-treated patients. Neither drug consistently abolished complex forms of ectopy [118].

A similar comparison was performed in 51 patients. 26 patients were randomized to the mexiletine group and 25 to the quinidine group. The drugs were administered in an increasing dose regimen to suppress the PVCs by 70 % from the baseline value in both groups. Mexiletine reduced the average number of PVCs by 70 % of the baseline number in a comparable fashion to quinidine; 69 % in the mexiletine group vs 70 % in the quinidine group ($p > 0.05$). There was a comparable reduction (≥ 50 %) of ventricular couplets from the baseline value in the 2 groups, 76 % in the mexiletine group vs 66 % in the quinidine group ($p > 0.05$). The effect of mexiletine on suppression of ventricular tachycardia was also similar, 72 % in the mexiletine group vs 71 % in the quinidine group ($p > 0.05$) [119].

The efficacy of combination therapy using a type IA agent (quinidine or procainamide) and mexiletine in suppressing inducible sustained ventricular tachyarrhythmias was studied in 3 patients undergoing serial drug testing with programmed stimulation. All patients had coronary artery disease (CAD) with previous myocardial infarction and abnormal left ventricular function (mean ejection fraction 35 %). Fifty-five percent of the patients presented with syncope or cardiac arrest. All 23 patients had inducible sustained ventricular tachyarrhythmias (18 had uniform morphology sustained ventricular tachycardia (VT) and 5 had ventricular fibrillation [VF]) during control electrophysiologic study, and therapy had failed with a type IA agent and mexiletine alone. The combination therapy of mexiletine and the type IA agent prevented induction of any ventricular tachyarrhythmias In 8 of 23 patients. In 15 patients, the combination significantly prolonged the tachycardia cycle length and reduced the symptoms associated with the induced arrhythmia [120].
Right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF) and wail motion score (WMS) were assessed in 14 patients with ventricular tachycardia before antiarrhythmic therapy, during mexiletine (MEX) and Q (quinidine) monotherapies and during combination therapy. During monotherapy, the daily doses and serum drug levels were: MEX: 621 mg/day and 3.4 μM/L; 1573 mg/day and 6.3 μM/L, respectively. With combination therapy, the daily doses and serum drug levels were: MEX 636 mg/day and 3.3 μM/L; 0, 1643 mg/day and 9.5 μM/L, respectively. Drug therapy did not affect group LVEF (drug free = 36±19 %, MEX = 34±18 %, Q = 36±19 %, and combination MEX-Q = 35 ± 12 %), RVEF (drug free = 34 ± 11 %, MEX = 35 ± 11 %, Q = 36 ± 13 %, and combination MEX- Q = 36 ± 12 %) or WMS. Ventricular function reserve was assessed in five patients. Drug therapy did not affect group exercise LVEF (drug free = 44 ± 14 %, MEX = 42 ± 12 %, Q = 43 ± 13 %, and MEX - Q = 45 ± 12 %), RVEF (drug free = 38 ± 10 %, MEX = 40 ± 11 %, Q = 39 ± 12 %, and MEX- Q = 40 ± 12 %), WMS, or exercise duration. Combination MEX-Q therapy did not have a significant effect on exercise performance or ventricular function in seven additional patients in whom no exercise studies were done during monotherapy. Thus, MEX-O combination therapy does not appear to depress ventricular function, at rest or during monotherapy [96].

The antiarrhythmic efficacy of oral mexiletine hydrochloride and quinidine sulphate were compared at 29 clinical centres in a double-blind, parallel-group trial involving 491 patients with benign or potentially lethal ventricular arrhythmias. Responders were defined as those who had at least a 70 % reduction in the frequency of ventricular premature complexes (VPCs) that persisted for 12 weeks, and who experienced no intolerable side effects that required discontinuation of therapy. The dose range used for mexiletine was 200 to 400 mg every 8 hours and that for quinidine 200 to 400 mg every 8 hours. More than half of the patients in each group were successfully treated with the smallest dose (200 mg every 8 hours mexiletine vs 200 mg every 8 hours for quinidine) [121].

Mexiletine has also been combined with flecainide and assessed in clinical studies. [redacted] administered the combination of mexiletine and flecainide in 11 patients in whom monotherapy with one of these drugs was ineffective for the suppression of inducible ventricular tachycardia or fibrillation. In eight of 11 studies, combination therapy prevented inducibility of a sustained ventricular tachycardia or resulted in induction 0f only non-sustained tachycardia (P = 0.0003, when compared to monotherapy). Seven patients received combination on the long term, for a mean of 18 months resulting in efficacy in suppressing inducible sustained ventricular tachycardia [122].

Mexiletine has been also combined with propranolol [123] or procainamide [137] in patients with inducible sustained ventricular tachycardia with, but with this therapy appeared to be of little value. On the other hand, when [redacted] combined class IC antiarrhythmic agents (encainide, propafenone or flecainide) concluded that although this combination does not often render the patient's ventricular tachycardia non-inducible, it causes in most patients further slowing of the rate of induced tachycardia, which may be of clinical importance [124]. The same was also supported by [redacted] with a combination of mexiletine and propafenone [125]. A recent successful treatment with a combination of mexiletine and nifekalant was reported which concluded in suppression of repetitive ventricular tachyarrhythmias [138].

The efficacy of mexiletine on ventricular arrhythmias was directly compared to those of disopyramide, aprindine and cibenzoline (single drug therapy) and additionally the efficacy of combination therapy of mexiletine with disopyramide (combination therapy) was studied by [redacted] 106 patients completed the protocol of the single drug therapy and 50 % or more reduction in the frequency of ventricular premature contractions (VPCs) was obtained in 24/43 (56 %) with disopyramide, in 24/44 (55 %) with mexiletine, in 18/29 (62 %) with aprindine and 10/18 (56 %) with cibenzoline. With mexiletine therapy 10/12 patients with fast VT rate showed a significant effect while only 4/12 patients with non-fast VT rate had a significant one. The combination therapy of mexiletine (100 mg t.i.d.) and disopyramide (50 mg t.i.d.) which was administered in 20 patients during hospitalization, showed approximately the same efficacy as disopyramide (100 mg t.i.d.) or mexiletine (150 mg t.i.d.) therapy alone [126].

Another comparison was performed between mexiletine and lidocaine in patients with ventricular premature depolarizations (VPDs). Twelve Patients received mexiletine intravenously at (5 to 10 mg/min) until ≥ 95 % VPD suppression was achieved or a total of 450 mg of drug was given. The average loading dose of mexiletine was 4.4 mg/kg, at an infusion rate of 0.1 mg/kg/min. Ten patients received lidocaine (1 mg/kg) given over 3 minutes, with a second similar bolus given if after 10 minutes ≥ 95 % VPD suppression was not achieved. Administration of mexiletine resulted in greater suppression of VPDs than administration of lidocaine in terms of mean percent reduction (96 % vs 68 %, $p < 0.01$) [127].

2.5.4.1.2 Open studies

The efficacy of mexiletine has been assessed by several studies since the 70s.

Efficacy was assessed by long-term tape-recording of electrocardiograms with computer analysis after administration to 59 patients with acute or chronic ventricular arrhythmias in the [redacted] Intravenous mexiletine successfully suppressed acute ventricular arrhythmias in 31 of 43 patients, with partial control in a further 9 [128]. The effects of mexiletine on ventricular dysrhythmias were also studied in 86 patients. 30 of the patients with acute myocardial infarction received mexiletine within forty-eight hours of the onset of symptoms. The findings of this study indicated that mexiletine, given intravenously or orally, is useful in the control of ventricular dysrhythmias, whether or not these are related to acute myocardial infarction, since a good response to the drug was obtained in 68 % of patients in whom its effects could be assessed [129].

Twenty-four patients with ventricular arrhythmias were treated with oral mexiletine (in the form of capsules containing either 200 or 50 mg) in the study of [redacted] for periods of from one to 16 months (total 10.4 patient-years). The usual starting dose was 400 to 600 mg, followed 4 to 6 hours later by the commencement of maintenance therapy at a dose of 150 to 350 mg. every 8 hours. In 19 patients arrhythmias were satisfactorily controlled and plasma levels previously shown to be within the therapeutic range were maintained on an 8 hourly regimen [130]. Another study that evaluated the long-term efficacy of mexiletine was performed by Campbell. Forty-eight patients with ischaemic heart disease received oral mexiletine for the control or prevention of ventricular arrhythmias. The most frequently used doses were 200, 250, and 300 mg 8-hourly. The treatment period varied from 2 days to more than 1 year (median 3 months). In more than one-half of the patients, no ventricular arrhythmias were detected [49]. The tolerability of those studies was good and this is also in agreement with the study of [redacted] which concluded in the safe profile of mexiletine given for a long time [139].

In another open study, mexiletine was administered during serial drug testing to 35 patients with electrically inducible ventricular arrhythmias and to 6 with recurrent ventricular tachycardia that could not be Induced or terminated by programmed cardiac stimulation. All patients had arrhythmias resistant to all conventionally available agents. Electrically induced arrhythmias were completely suppressed during mexiletine therapy in 13 patients. In 12 patients no antiarrhythmic regimen was completely suppressive and in 7 of these mexiletine favorably modified the response to programmed stimulation. In four of six patients with frequent episodes of spontaneous ventricular tachycardia that were not inducible by programmed cardiac stimulation, arrhythmia was controlled by mexiletine. The presence of complete arrhythmia suppression with mexiletine during acute testing accurately predicted long-term freedom from recurrent arrhythmia in 16 of 17 patients over a mean follow-up period of 12.6 ± 6 months. This study proved that mexiletine is effective in patients resistant to conventional drugs [131], although the study of [redacted] reported that mexiletine has limited efficacy in the treatment of chronic drug-refractory ventricular arrhythmias and the chance of success with mexiletine is higher in patients who have never failed antiarrhythmic therapy [140].

[redacted] demonstrated that acute intravenous and short-term oral mexiletine (200 mg) therapy was effective in suppressing the arrhythmia in six of eight patients with recurrent ventricular tachycardia. Five of the six patients who were placed on maintenance therapy remained asymptomatic during a mean follow-up of 15 months [141]. This study showed that long-term suppression of ventricular tachycardia can be predicted by the combined acute and short-term effects of mexiletine.

[redacted] examined the effects of mexiletine on LV and right ventricular (RV) function. To determine the hemodynamic effects of mexiletine, LV and RV ejection fraction (EF) were measured by radionuclide ventriculography in 10 patients with LV dysfunction (LVEF <50 %). Symptom-limited exercise tests were also performed. Patients were studied before and during therapy with oral mexiletine. Patients were studied before and during therapy with oral mexiletine and there was no significant change in LVEF (28 % vs 27 %) or RVEF (46 % vs 41 %) [95]. The same group has also concluded that if therapy with mexiletine is carefully evaluated and individualized, the drug is effective and well-tolerated during long-term use [142].

In 58 patients, to whom conventional drugs had been unsuccessful, different doses of mexiletine were administered, ranging from 250 mg to 1500 mg (mean 652 mg) with mean duration of therapy 14.4 months. Mexiletine was associated with a decrease of 52 % in total premature ventricular complexes in 24 hours compared with control (6,841 ± 1,053 [SEM] versus 3,248 ± 734, $P < 0.005$) and 19 patients (36.5 %) had a greater than 83 % decrease in ventricular ectopic rhythm. The drug was discontinued in 6 of these 19 patients since 5 of them (26 %) experienced side effects after a mean period of 29.6 weeks (range 0.83 to 63.2) and sudden death occurred in 1 patient (5 %); this indicates effective suppression of ventricular ectopic rhythm without significant side effects in 13 (25 %) of 52 patients during long-term therapy [132]. Adjustment of drug dosage to achieve therapeutic blood levels resulted in an efficacy on ventricular ectopic rhythm similar to that obtained with the maximal tolerated dose. Mexiletine was associated with a 48 % decrease in episodes of ventricular tachycardia (345.5 versus 179.3/24 h) and 5 of 10 patients with a history of cardiac arrest remained free of symptomatic ventricular tachyarrhythmias for 14.8 months (range 3.7 to 24.3). In 12 patients left ventricular ejection fraction, determined by radionuclide angiography before and during mexiletine therapy, demonstrated no significant change (32 versus 34 %) [132].

The overall experience with 138 patients receiving mexiletine for chronic drug-resistant ventricular arrhythmias was reported by [redacted] Of these 138 patients, 26 (19 %) were "early failures" (experiencing refractory arrhythmias or intolerant to therapy prior to initial hospital discharge) and an additional 22 patients (16 %) were "late failures" (experiencing refractory arrhythmias or intolerant to therapy after hospital discharge). Chronic oral maintenance therapy was successful for 90 patients (65 %). Nine (7 %) arrhythmia-related deaths occurred [33].

One hundred patients with a 70 % or greater reduction of ventricular premature contractions (VPCs) from baseline during 12 weeks of mexiletine therapy were continued on treatment for an additional 9 months. The most frequently used dosage of mexiletine during each 3-month treatment period was 600 mg/day (50.0-55.6 % of patients) and concluded that long-term mexiletine administration for non-life-threatening ventricular arrhythmias was effective and well tolerated [133].

The antiarrhythmic efficacy of mexiletine 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 non-sustained 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 non-sustained ventricular tachycardia were suppressed in only 16 % of the cohort [143].

The long term effect of mexiletine on left ventricular (LV) contractility in patients with congestive heart failure was examined by [redacted]) contractility was measured before and after continuous oral administration of mexiletine in 8 patients with congestive heart failure accompanied by mitral regurgitation (MR) using Doppler echocardiography. The left ventricular ejection fraction and the left ventricular and left atrial dimensions also were unchanged. These findings indicate that continuous oral administration of mexiletine has no effect on LV contractility in patients with congestive heart failure [144].

The efficacy of mexiletine in patients with recurrent ventricular tachyarrhythmias and/or electrical storm events, in whom standard treatment strategies failed to prevent ventricular tachyarrhythmia was recently evaluated by [redacted] The authors performed a retrospective cohort analysis of all patients treated with mexiletine for recurrent ventricular tachycardia and/or ventricular fibrillation in their institution. The median time of mexiletine treatment was eight months. The mexiletine dose was 600 mg/day in 13 patients and 400 mg/day in four patients. Treatment with mexiletine significantly reduced the number of electrical storm events (14 episodes 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 interventions vs. nine interventions; median and IR for 17 patients: 10 [5–25] vs. 0 [0–2], p = 0.0006), in comparison with a matched period before initiation of treatment [145].

The efficacy of intravenous mexiletine and a method for converting from intravenous to oral mexiletine therapy was evaluated by [redacted] in Fifteen patients with repetitive ventricular ectopy (13 had ventricular tachycardia). Patients received intravenous mexiletine at a rate of 10 mg/min for 30 to 60 minutes. Ventricular ectopy was suppressed with minimal side effects in 10 of 15 subjects. Oral mexiletine was begun immediately after completion of the intravenous infusion at a dose of 10 mg/kg/day in the 10 responders to intravenous therapy. In eight, the oral dose was effective in suppressing the arrhythmia, but it induced side effects in three of them. In one of these three, dose reduction resulted in adequate arrhythmia control with acceptable toxicity. In the two who did not respond to the original dose, a larger dose (15 mg/kg/day) induced arrhythmia control with acceptable side effects in one subject. Thus rapid control of non-sustained repetitive ventricular arrhythmia can be achieved with intravenous mexiletine in about two thirds of patients, and conversion to oral therapy can often be achieved smoothly without significant arrhythmia recurrence [134].

The beneficial effect of mexiletine in cardiac arrhythmias was also demonstrated in patients with chronic obstructive pulmonary disease. The results of the study showed that mexiletine limited cardiac arrhythmias in patients with heart and respiratory failure [146].

2.5.4.1.3 Reviews

[redacted] performed a meta-analysis and reported the effectiveness of antiarrhythmic drugs for the suppression of ventricular ectopic depolarizations [147].

2.5 Clinical overview

Table XV Rank and likelihood of obtaining 80 % or more suppression of ventricular ectopic depolarizations with each antiarrhythmic drug [147]

Rank	Drug	Likelihood of response (%)	Patients treated (n)	Studies (n)
1	Amiodarone	90 (86-93)	115	5
2	Nortriptyline	84 (66-94)	16	1
3	Indecainide	82 (68-91)	31	3
4	Encainide	80 (71-87)	125	5
5	Flecainide	79 (70-86)	230	8
6	Propafenone	74 (64-81)	187	10
7	Imipramine	74 (56-86)	22	1
8	Pirmenol	73 (49-89)	12	1
9	Lorcainide	69 (59-78)	136	7
10	Moricizine	68 (57-77)	143	8
11	Atenolol	64 (43-81)	20	1
12	Cibenzoline	61 (47-73)	86	3
13	Perhexiline	58 (45-95)	24	1
14	Quinidine	53 (43-63)	446	17
15	Disopyramide	51 (40-62)	161	10
16	Sotalol	51 (38-64)	72	3
17	Procainamide	48 (36-60)	109	5
18	Ajmaline derivatives	46 (32-60)	47	3
19	Acebutolol	42 (31-53)	305	11
20	Propranolol	41 (31-53)	179	7
21	**Mexiletine**	**41 (31-52)**	**214**	**11**
22	Metoprolol	41 (24-62)	20	7
23	Tocainide	39 (29-50)	180	8
24	Acecainide	37 (26-49)	27	2
25	Naodolol	28 (18-42)	58	2
26	Phenytoin	17 (4-49)	10	1
27	Verapamil	0 (0-93)	14	1

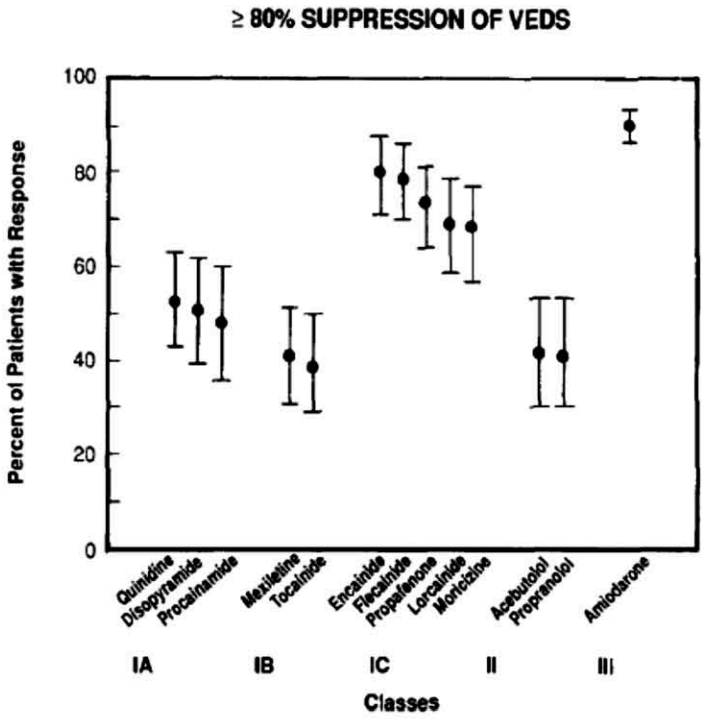


Figure 14 Mean percentage of patients and 95 % confidence interval (± 1.4 × standard error) on each antiarrhythmic drug with ≥ 80 % suppression of total ventricular ectopic depolarizations. Only those drugs studied in ≥ 100 patients in ≥ 5 studies are included [147]

Table XVI Likelihood of obtaining 100 % suppression of non-sustained ventricular tachycardia with each antiarrhythmic drug [147]

Rank	Drug	Likelihood of response (%)	Patients treated (n)	Studies (n)
1	Amiodarone	100 (0-100)	24	2
2	Propafenone	92 (67-98)	74	8
3	Flecainide	82 (47-96)	90	4
4	Disopyramide	82 (42-97)	9	2
5	Lorcainide	80 (39-96)	13	2
6	Moricizine	79 (36-96)	12	2
7	Indecainide	78 (37-96)	18	2
8	Cibenzoline	77 (38-95)	47	3
9	Nortriptyline	77 (28-96)	11	1
10	Pirmenol	67 (23-93)	9	1
11	Encainide	66 (27-91)	30	3
12	Ajmaline derivatives	65 (27-90)	22	3
13	Procainamide	64 (26-90)	41	3
14	Nadolol	63 (21-92)	13	1
15	Quinidine	57 (21-92)	158	9
16	Tocainide	51 (17-84)	65	4
17	**Mexiletine**	**50 (17-84)**	**52**	**5**
18	Metoprolol	49 (13-86)	10	1
19	Propranolol	47 (14-83)	37	5
20	Acebutolol	47 (14-83)	35	4

2.5.4.2 OTHER USES

2.5.4.2.1 Myotonia

Myotonia congenita is characterized by muscle stiffness present from childhood; all striated muscle groups including the extrinsic eye muscles, facial muscles, and tongue may be involved. Muscle stiffness may respond to sodium channel blockers such as mexiletine [148].

Treatment of the muscle stiffness is only indicated if the myotonia compromises the every-day life or when reduction of symptoms is required for professional or social activities. Therapy of first choice is mexiletine (2 - 3 × 200 mg/ day) [149].

[redacted] were that used mexiletine for myotonia treatment. Improvement of the electrophysiologic abnormalities with mexiletine was documented corresponding with clinical improvement. Mexiletine was reported to be highly effective in preventing cold induced paralysis in paramyotonia and in relieving myotonia in myotonia fluctuans and myotonia permanens but failed to relieve attacks of hyperkalaemic periodic paralysis.

[redacted] supported that the effect of mexiletine depends on the probability of a channel assuming a certain state or undergoing a certain interstate transition. The type of mutation, the extracellular pH and the membrane potential all determine this probability and thus the effectiveness of treatment even when the binding site remains unaltered [152].

Mexiletine has been found to be effective for paramyotonia congenita, potassium aggravated myotonia, long QT– 3 syndrome, and neuropathic pain [153]. This drug elicits tonic block of Na^+ channels when cells are stimulated infrequently and produces additional use-dependent block during repetitive pulses. It was proved that the in vivo efficacy of mexiletine is primarily due to the open-channel block of persistent late Na^+ currents, which may arise during various pathological conditions.

One randomized study suggested that mexiletine at 400 to 600 mg daily is a safe and effective anti-myotonia medication [154].

[redacted] suggested that mexiletine at oral dosages of 150 – 200 mg t.i.d. may be considered as an effective, symptomatic treatment in patients with DM1 with functionally significant myotonia and appears to be safe in the short term [155].

It has been reported by [redacted] that mexiletine is the agent of first choice for DM1 [156]. There are some case reports and studies on the use of mexiletine in people with myotonia [157]. [redacted] conducted a randomized, double-blind, placebo-controlled two-period crossover study in 59 patients with NDM [158]. Mexiletine significantly improved patient-reported stiffness on the IVR (interactive voice response diary). Mexiletine improved the INQoL QOL score (mexiletine 14.0, placebo 16.7, difference −2.69, 95 % CI −4.07, −1.30, P<0.001) and decreased handgrip myotonia on clinical exam (seconds: mexiletine 0.164, placebo 0.494, difference −0.330, 95 % CI −0.633, −0.142, P<0.001). The most common adverse effect was gastrointestinal (9 mexiletine, 1 placebo). Two participants experienced transient cardiac effects that did not require stopping the study (1 placebo, 1 mexiletine). One serious adverse event was determined to be not study-related. This study provided evidence of the effectiveness of mexiletine for patients with myotonia.

[redacted] investigated the effects of mexiletine on excitability of human axons in vivo [159]. They reported a reduction in pain/muscle cramps, associated with decreased strength-duration time constants, increased rheobasic currents and lower refractoriness, all of which were consistent with reduced nodal Na^+ currents. They concluded that oral mexiletine in a dosage of 300 mg daily suppresses persistent Na^+ currents in human motor axons.

Mexiletine was administered also to patients with dystonia who had failed to respond to previous pharmacotherapy, at a dose of 200 mg/day orally and increased up to a maximum dose of 800 mg/day. At the end of a six-week period, a significant improvement in the rating scale for dystonia was observed after mexiletine treatment [160].

A new neurophysiological test (3 Hz-PNRS) was used to detect indirectly and quantify the clinical phenomenon of the TW (Transient Weakness) that occurs in myotonic syndromes due to CLCN1 (Human Skeletal Muscle Chloride Channel) mutations. The benefit of mexiletine was assessed by using the abovementioned test [161]. Mexiletine induced a reduction of TDN (Transitory Depression) from -51.6 % to -28.8 % after treatment.

Recently, [redacted] investigated the cause of transient weakness in myotonia congenita (MC) and the mechanism of action of mexiletine in reducing weakness. The changes in neuromuscular excitability produced by 1 minute of maximal voluntary contractions (MVC) were measured on the amplitude of compound muscle action potentials (CMAP) in two patients with either recessive or dominant MC, compared to control values obtained in 20 healthy subjects and the measurements were performed again in MC patients after mexiletine therapy. Transient reduction in maximal CMAP amplitude lasting several minutes after MVC was evident in MC patients, whereas no change was observed in controls. Mexiletine efficiently reduced this transient CMAP depression in both patients [162].

The review of [redacted] evaluated a series of double-blind, randomized, placebo-controlled trials and genetically confirmed nondystrophic myotonia adult patients were enrolled in these studies. Mexiletine (600 mg daily) or placebo were administered to the patients. In 24 of the 27 completers, a clinically meaningful treatment effect was found. Mexiletine resulted in a 100 % posterior probability of reaching a clinically meaningful reduction in self-reported muscle stiffness for the nondystrophic myotonia group overall and the CLCN1 genotype subgroup and 93 % posterior probability for the SCN4A genotype subgroup. In the total nondystrophic myotonia group, the median muscle stiffness score was 6.08 (interquartile range, 4.71-6.80) at baseline and was 2.50 (95 % credible interval [CrI], 1.77-3.24) during the mexiletine period and 5.56 (95 % CrI, 4.73-6.39) during the placebo period; difference in symptom score reduction, 3.06 (95 % CrI, 1.96-4.15; n = 27) favoring mexiletine [163].

2.5.4.2.2 Neuropathic Pain

The first successful use of mexiletine in a patient with neuropathic pain due to malignant nerve root compression was reported by [redacted] [164]. Three patients with neuropathic pain reported also decreased VAS scores when mexiletine was added to their analgesic regimen in the study of [redacted] [165].

Twenty subjects suffering from neuropathic pain with prominent allodynia were enrolled in the randomized placebo-controlled crossover study of [redacted] Patients were titrated to a maximum dose of 900 mg/day or dose-limiting side effects, whichever occurred first. At baseline and on days 0,

4, 7, and 10, the following tests were performed: (1) Quality of Life Questionnaires; (2) pain scores; (3) area of allodynia; (4) side effects; (5) neurosensory testing; and (6) peak and trough plasma mexiletine levels. The authors reported that there was a significant effect of mexiletine on stroking-induced pain, however higher doses would be more beneficial [166].

The changes in axonal persistent Na^+ currents in patients with neuropathic pain and the effects of mexiletine on axonal excitability properties were examined by [redacted] The technique of latent addition was used to estimate nodal persistent Na^+ currents in superficial radial sensory axons of 17 patients with neuropathic pain/paresthesias before and after mexiletine treatment. Brief hyperpolarizing conditioning currents were delivered, and threshold change at the conditioning-test interval of 0.2 ms was measured as an indicator of the magnitude of persistent Na^+ currents. Threshold changes at 0.2 ms in latent addition were greater in the neuropathic patients than in the normal controls ($p < 0.001$). After mexiletine treatment, there was a reduction in clinical pain scores ($p < 0.001$), associated with decreased threshold changes at 0.2 ms ($p < 0.001$) [167].

The following randomized controlled studies on oral mexiletine in neuropathic pain were included in the review of [redacted]) [168].

Table XVII Randomized and controlled studies on oral mexiletine in neuropathic pain [168]

Condition	Number of patients per treatment arm	Design & duration of each treatment	Dose & Comparison	Outcome	Ref.
Peripheral nervous system damage/disease	n = 11 (male)	crossover, D-B, > 4 weeks	mexiletine up to 750 mg/d vs PL	Mexiletine 750 mg/d significantly Different from PL; dose response	[169]
Neuropathic pain	n = 20	crossover, D-B, 10 days	mexiletine up to 900 mg/d vs PL	Significant effect of mexiletine on stroking-induced pain but not on any other pain scores	[166]
HIV neuropathy	n = 47-50 (94-98 % male)	parallel group, D-B, 8 weeks	mexiletine up to 600 mg/d vs amitriptyline up to 100 mg/d vs PL (benztropine up to 0.5 mg/d)	Neither mexiletine nor amitriptyline was significantly different from PL	[170]
HIV neuropathy	n = 22	crossover, D-B?, 6 weeks	mexiletine up to 600 mg/d vs PL	No significant difference	[171]
Diabetic neuropathy	n = 16	crossover, D-B, 4 weeks	mexiletine 750 mg/d vs PL	Mexiletine produced significant pain relief	[172]
Diabetic neuropathy	n = 31-33	parallel group, D-B, 3 weeks	mexiletine 225 mg/d vs mexiletine 450 mg/d vs mexiletine 675 mg/d vs PL	Significant reduction of pain at nighttime on mexiletine 675 mg/d vs PL, no other significant differences, no correlation between plasma concentration of mexiletine and therapeutic effect	[173]
Diabetic neuropathy	n = 14-15	parallel group, D-B, 3 weeks	mexiletine 600 mg/d vs PL	No difference	[174]
Diabetic neuropathy	n = 47-48	parallel group, D-B?, 6 weeks	mexiletine 450-675 mg/d vs PL	No overall pain relief. Significant effect in subgroups (burning, stabbing and heat sensations)	[175]

The recent meta-analysis of [redacted] included 24 randomized controlled trials and compared the mean differences for primary efficacy (reduction in all pain), secondary efficacy (reduction in moderate

or severe pain) and primary safety for first-line therapies for chronic pain. Mexiletine and ketamine ranked highest in primary efficacy and considering all parameters evaluated, mexiletine and nefopam can be considered as first line therapies for the prevention of chronic post-surgical pain (Figure 15 and Figure 16) [176].

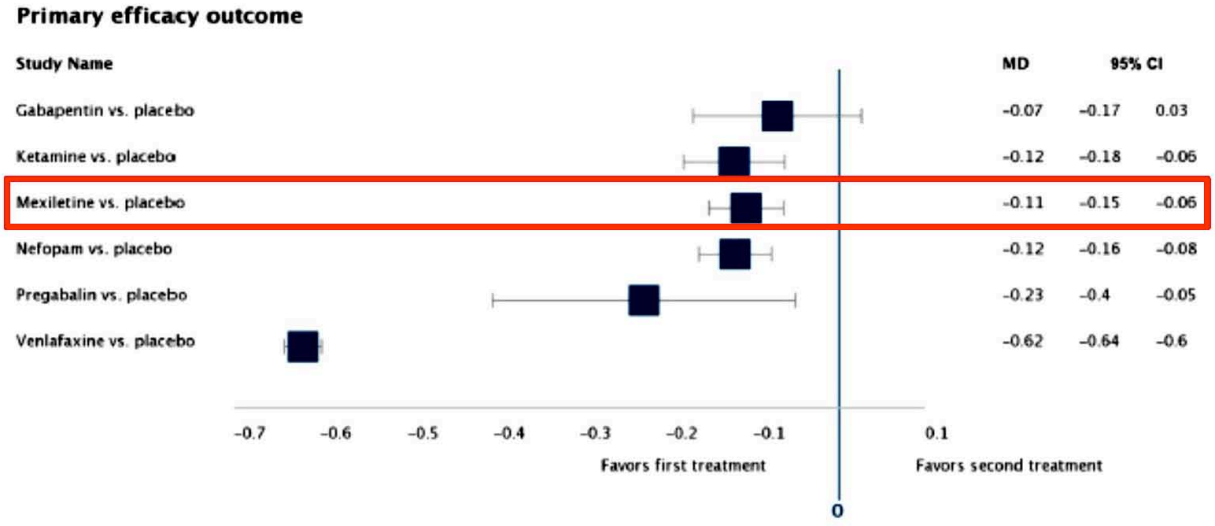


Figure 15 Forest plot of the mean difference (MD) and associated 95 % confidence intervals (95 % CIs) comparing each treatment with placebo for the primary efficacy outcome [176]

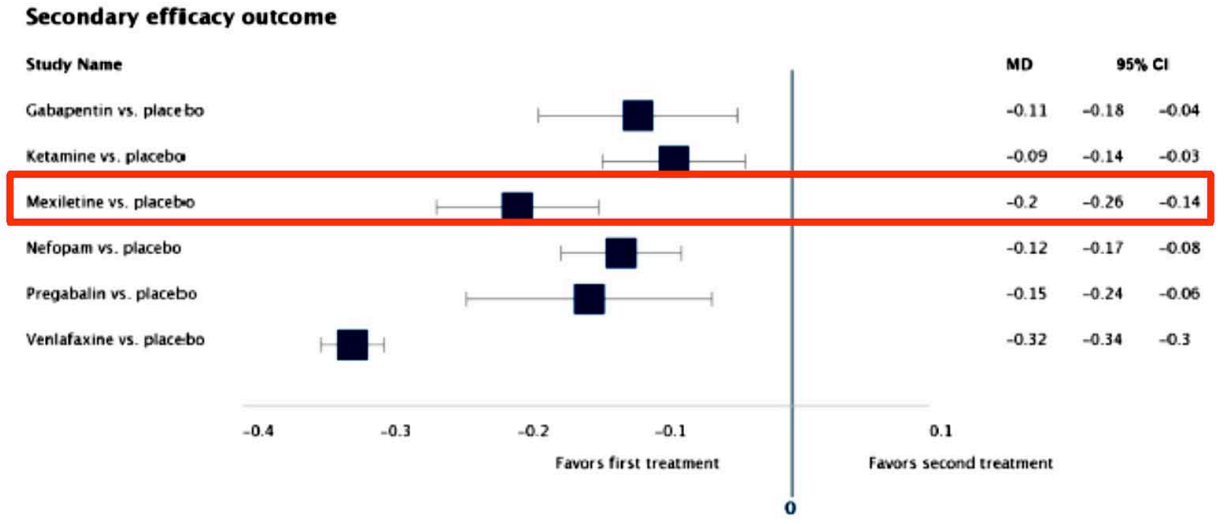


Figure 16 Forest plot of the mean difference (MD) and associated 95 % confidence intervals (95 % CIs) comparing each treatment with placebo for the secondary efficacy outcome [176]

2.5.4.3 DOSAGE AND ADMINISTRATION

Plasma elimination half-life may be prolonged in moderate to severe hepatic disease, and in patients with a creatinine clearance of less than 10 ml/min. Therefore, individual dose titration is advised in these conditions.

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

2.5.4.3.1 Standard loading dose regimen

Loading dose: Initially, if more rapidly effective blood levels are required, a loading dose, usually 400 mg may be desirable.

Maintenance dose: 200-250 mg of Mexiletine Hard Capsules are given three to four times daily commencing 2 hours after the loading dose. The usual daily dose is between 600-800 mg in divided doses. Optimal doses range from 300-1200 mg daily in divided doses.

Mexiletine Hard Capsules are absorbed in the upper part of the small intestine. In acute myocardial infarction and particularly when opiates have been given, rate of absorption but not bioavailability may be delayed and therefore, a larger loading dose e.g. 600 mg may be preferable.

2.5.4.3.2 Alternative loading dose regimes

Combination IV Mexiletine and oral Mexiletine loading dose: IV injection of 200 mg Mexiletine hydrochloride Solution for Injection/Infusion is given at a suggested rate of 25 mg per minute. On completion of injection or infusion 400 mg of Mexiletine Hard Capsules are given orally.

Combination IV lidocaine (lignocaine) and oral Mexiletine loading dose: IV lidocaine (lignocaine) is given according to manufacturer's instructions. On completion of injection 400 mg of Mexiletine Hard Capsules are given orally.

2.5.4.3.3 Change over from IV to oral maintenance

On discontinuing the IV infusion commence the maintenance dose. The first capsule should be taken at, or shortly before, the end of the infusion (an oral loading dose should not be given). 200 – 250 mg of Mexiletine Hard Capsules are given orally three or four times a day.

2.5.5 OVERVIEW OF SAFETY

2.5.5.1 TOXICITY

2.5.5.1.1 Adverse Events

Generally side effects are of five types:

Gastro-Intestinal: Nausea, vomiting, indigestion, constipation, diarrhoea, dry mouth, unpleasant taste, hiccoughs [93]. Oesophageal ulceration may occur if oral mexiletine is swallowed without adequate liquid and is lodged in the oesophagus [177].

Central Nervous System: Drowsiness, dizziness, diplopia, blurred vision, nystagmus, dysarthria, ataxia, tremor, paraesthesia, convulsion, psychiatric disorders, confusional state, insomnia [93].

Cardiovascular: Hypotension, sinus bradycardia, atrial fibrillation, palpitation and conduction defects. Exacerbation of arrhythmias [178], pre-existing heart failure and torsade de pointes [179].

Pulmonary infiltrates, interstitial lung disease and pulmonary fibrosis have been observed in isolated cases [180].

Blood and lymphatic: Rash, arthralgia, fever, thrombocytopenia and appearance of positive but symptomless antinuclear factor titres. Leukopenia has been observed rarely. Rare cases of Stevens-Johnson syndrome, some with liver involvement, have been reported in Japan. Isolated cases of erythroderma have also been reported [181].

Hepatobiliary disorders: Liver damage has been observed following mexiletine administration; jaundice has been reported [182].

Immune system: Drug reaction with eosinophilia and systemic symptoms [183].

Other and unspecified Allergy: DRESS (Drug Reaction with Eosinophilia) has been reported after mexiletine administration [183].

Ear and labyrinth disorders: Vertigo has been reported as adverse event in several clinical trials [139, 184].

General disorders: Generalized malaise has been reported after mexiletine administration in patients with refractory ventricular arrhythmias [185].

In a placebo-controlled study the following major adverse effects have been reported:

Table XVIII Major Adverse Experiences among 12 Patients Treated With Mexiletine and Placebo [101]

Adverse Effects	Patients (n)	
	Mexiletine Therapy (n = 12)	Placebo Therapy (n = 11)
Digestive		
Nausea	2	0
Diarrhoea	0	3
Indigestion	4	0
Burning stomach	1	0
Bad taste in mouth	0	1
Stomach ache	1	0
Total	8	4
Central nervous system		
Dizziness	3	6
Fatigue	2	2
Light headedness	3	0
Headache	2	3
Nervousness	1	1
Total	7	5

In the study of [redacted], after administration of mexiletine to 15 patients with chronic and recurrent episodes of ventricular tachycardia or ventricular fibrillation. Adverse side effects occurred in nine patients (60 %) and were severe enough to necessitate discontinuation of therapy in six patients (40 %). Side effects were mostly gastrointestinal (nausea and vomiting) and CNS effects (dizziness, tremor, ataxia) and appeared to be dosage-related [92].

During long-term mexiletine therapy in 107 patients with ventricular arrhythmia and an average follow up of 22.8 months, side effects occurred in 13 patients after an average of 5.1 months and were primarily gastrointestinal and neurologic [142]. Similarly, in the study of [redacted] adverse reactions were attributed to mexiletine in 31 (65 %) of the 48 patients. After excluding those in whom other possible causes of the adverse effects might have operated, 26 (54 %) of the 48 patients had adverse effects. The most common side effects were tremor, nausea, and dyspepsia [49].

As previously reported, mexiletine is absorbed in the upper part of the small intestine. In acute myocardial infarction and particularly when opiates have been given, rate of absorption but not bioavailability may be delayed and therefore, a larger loading dose e.g. 600 mg may be preferable. However, [redacted] has reported that no favourable trend in mortality was observed as a result of mexiletine therapy and by increasing mexiletine dose, more serious adverse effects are expected [107].

For mexiletine, increased plasma concentrations and prolonged half-life in patients with cardiac failure and after acute myocardial infarction and therefore should be avoided [179].

2.5.5.1.2 Pregnancy and Lactation

Mexiletine freely crosses the placenta. Therefore, mexiletine should only be used in pregnancy if the potential benefit justifies the potential risk. Mexiletine appears in breast milk in concentrations, which may have an effect on the infant. Therefore, if the use of mexiletine is deemed essential for the mother, an alternative method of infant feeding should be considered [186].

Although teratogenicity has not yet been linked to mexiletine and reports demonstrating the drug's successful use in women during pregnancy exist [186, 187], data during pregnancy are limited [187]. 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 [188].

2.5.5.1.3 Overdose

Fatal outcomes have been reported for acute overdoses at 4.4 g of mexiletine hydrochloride ingestion [189], but survival has also been reported following acute overdose of approximately 4 g of oral mexiletine hydrochloride [190].

The symptoms of mexiletine overdose include neurological disorders (paresthesia, confusion, hallucination, seizure) [191, 192] and cardiac disorders (sinusal bradycardia, hypotension, collapse, and in extreme cases, cardiac arrest) [179].

The management of overdose is mainly symptomatic.

2.5.5.2 DRUG INTERACTIONS

A list of the major drug-drug interactions involving mexiletine is given in Table XIX.

Table XIX: Drug interactions with mexiletine [193]

Agent	Interaction	Management
Enzyme inducers (phenytoin, phenobarbital, rifampicin) [194, 195]	↓ in plasma mexiletine concentrations with a loss of efficacy	Monitor for mexiletine efficacy and adjust dosage as needed
Ritonavir [196]	↑ in plasma mexiletine concentrations due to inhibition of CYP2D6	Monitor for mexiletine toxicity
Amiodarone [196]	↑ in plasma mexiletine concentrations due to inhibition of CYP2D6	Monitor for mexiletine toxicity
Quinidine [196]	↑ in plasma mexiletine concentrations due to inhibition of CYP2D6	Monitor for mexiletine toxicity
Theophylline [197-204]	↑ in plasma theophylline concentrations	Monitor theophylline concentrations and adjust dosage as needed
Selective serotonin reuptake inhibitors [205]	↑ in plasma mexiletine concentrations due to inhibition of CYP2D6	Monitor for mexiletine toxicity

2.5.5.2.1 Pharmacodynamic Interactions

2.5.5.2.1.1 Antiarrhythmics inducing torsades de pointes (Class Ia, Ic, III antiarrhythmics)

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. The concomitant use of mexiletine and antiarrhythmic medicines inducing torsades de pointes is contraindicated [206-208].

2.5.5.2.1.2 Other antiarrhythmics (Class Ib, II, IV antiarrhythmics)

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) is not recommended, unless exceptionally to balance the arrhythmic risk and the risk caused by therapy, because of the increased risk of adverse cardiac reactions [209].

2.5.5.2.2 Pharmacokinetic Interactions

2.5.5.2.2.1 Effect of other medicinal products on Mexiletine

CYP1A2 & CYP2D6 inhibitors

Co-administration of mexiletine with a hepatic enzyme inhibitor (CYP1A2 inhibitor: ciprofloxacin, fluvoxamine, propafenone; CYP2D6 inhibitor: propafenone, quinidine) significantly increases mexiletine exposure and thus the associated risk of adverse reactions to mexiletine [210].

In a single-dose interaction study, the clearance of mexiletine was decreased by 38 % following the co-administration of fluvoxamine, an inhibitor of CYP1A2. Therefore, clinical and ECG monitoring, as well as adaptation of mexiletine dosage may be indicated throughout and after treatment with a CYP1A2 or CYP2D6 inhibitor [211].

CYP1A2 & CYP2D6 inducers

Co-administration of mexiletine with a hepatic enzyme inducer (CYP1A2 inducer: omeprazole; CYP2D6 inducer: phenytoin, 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 [195, 210, 212].

In a clinical study, co-administration of mexiletine with phenytoin resulted in a significant decrease in exposure to mexiletine ($p < 0.003$) due to enhanced clearance as reflected in significantly decreased elimination half-life (17.2 to 8.4 hours, $p < 0.02$). Therefore, based on the clinical response, the mexiletine dosage should be adapted during and after treatment with the enzyme inducer [195].

After the oral administration of single (167 mg) and multiple (83 mg twice a day during 8 days) doses of mexiletine, total clearance of mexiletine is significantly increased in smokers (1.3 to 1.7-fold) due to induction of CYP1A2, resulting in a correspondingly decreased elimination half-life and drug exposure. Mexiletine dose may need to be increased if a patient starts to smoke during mexiletine treatment and decreased if a patient stops smoking [72].

2.5.5.2.2.2 Effect of Mexiletine on other medicinal products

CYP1A2 substrates

Mexiletine is a potent inhibitor of CYP1A2; therefore, co-administration of mexiletine with medicinal products metabolised by CYP1A2 (such as theophylline, caffeine, lidocaine or tizanidine) [197-201, 204] 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, e.g. theophylline and tizanidine [50, 73].

Caffeine

In a clinical study in 12 subjects (5 healthy subjects and 7 patients with cardiac arrhythmias), the clearance of caffeine was decreased by 50 % following the administration of mexiletine. Increased concentrations of caffeine occurring with the co-administration of mexiletine may be of concern in patients with cardiac arrhythmia. It is, therefore, recommended to reduce caffeine intake during treatment with mexiletine [213].

OCT2 substrates

The organic cation transporter 2 (OCT2) provides an important pathway for the uptake of cationic compounds in the kidney. Mexiletine may interact with drugs transported by OCT2 (such as metformin and dofetilide) [214].

If mexiletine and other OCT2 substrates are to be used concurrently, the OCT2 substrate blood levels should be monitored, particularly when the mexiletine dose is changed [214].

Substrates of other enzymes and transporters

No clinically significant interactions between mexiletine and digoxin have been reported. The effects of mexiletine on digoxin concentrations were studied in patients and healthy volunteers. Steady-state concentrations of digoxin were not altered by the addition of mexiletine.

No formal studies to define the effect of mexiletine on serum warfarin concentration and prothrombin time have been conducted. Although mexiletine is marketed and commonly used in several countries, no reports of substantive changes of prothrombin time during mexiletine treatment have appeared. It seems unlikely that an interaction with oral anticoagulants is common or large [50, 210].

2.5.6 BENEFITS AND RISKS CONCLUSIONS

2.5.6.1 THERAPEUTIC CONTEXT

2.5.6.1.1 Disease or Condition

Ventricular arrhythmia is a primary cause of mortality and morbidity in patients with cardiac diseases. Therapy for ventricular arrhythmias is guided by the estimated risk of sudden death posed by the arrhythmia, the likelihood of recurrence, symptoms, and the risks and benefits of therapies. Associated underlying heart disease and nature of the arrhythmia substrate are important considerations and is often suggested by the electrocardiographic (ECG) characteristics of the arrhythmia.

2.5.6.1.2 Current Therapies

Class I agents are sodium channel blockers, further dived into Class IA (quinidine, procainamide and disopyramide), Class IB (lidocaine, mexiletine), and Class IC (flecainide, propafenone). Class II agents are beta-adrenergic receptor blockers, such as propranolol. Class III agents are potassium channel blockers, such as amiodarone, sotalol, dofetilide, and dronedarone.

In the early 70s, Mexiletine was approved in Europe by Boehringer as Mexiletine capsules at strengths of 50 mg, 100 mg and 200 mg and as solution for injection and was indicated for the treatment of ventricular arrhythmias which is considered as life-threatening. It has been examined alone or in combination with other antiarrhythmic agents in several clinical trials.

Currently, there is no licensed mexiletine product in the UK for the treatment of ventricular arrhythmias, [redacted]

2.5.6.2 BENEFITS

Several studies from early 70s have reported that Mexiletine is well absorbed from the GI tract and unlike lidocaine its first-pass metabolism is low.

Combination with other antiarrhythmic drugs, particularly of Class IA, has improved the response rate. Although this response rate is no better than that with other anti-arrhythmics, and mexiletine may be less effective than drugs such as amiodarone, flecainide and propafenone, mexiletine has several advantages over alternative drugs. It has no significant haemodynamic effects and usually does not adversely affect already compromised left ventricular function in patients with cardiomyopathy or AMI, as assessed using radionuclide ventriculography. Many anti-arrhythmic drugs have a negative inotropic effect in such patients, limiting their usefulness in a large proportion of patients at serious risk of developing ventricular arrhythmias.

Mexiletine does not prolong QRS or QT (QTc) intervals (and may reverse the effects of quinidine in this respect), and it appears to have a low propensity for pro-arrhythmic effects, although direct comparative results are lacking.

2.5.6.3 RISKS

The 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. The incidence of adverse effects for which treatment has to be stopped in the medium to long term is in the range 7 to 35 %.

Non-cardiac effects are common with mexiletine therapy. Such effects include tremor, diplopia, nausea and vomiting and occur in up to 70 % of patients. 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.

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 AMI, congestive heart failure or conduction disturbance (with careful monitoring).

2.5.6.4 BENEFIT-RISK ASSESSMENT

The pharmacodynamics and pharmacokinetics of mexiletine are well established, both in healthy subjects and patients with different disease states, after both intravenous and oral administration. The studies included in the present document can support the well-known pharmacokinetic, pharmacodynamic and safety profile of Mexiletine.

Additionally, in order to bridge the proposed formulation with literature data, the applicant performed one clinical study to compare the bioavailability of the proposed product with the bioavailability of currently available products and literature data. The results of the study indicated that the proposed product exhibits comparable rate and extent of absorption with the data available on the public domain. Most of these data have been generated using the historical reference product (Mexitil), and therefore its efficacy and safety profile can be extrapolated to the proposed formulation.

A second bridge is build based on the pharmaceutical equivalence of the proposed formulation with the historical reference product. In [redacted]

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.

2.5.6.5 APPENDIX

2.5.6.5.1 Pharmacokinetic data of mexiletine – Literature data

Table XX Pharmacokinetic data of mexiletine after oral administration (literature data)

Ref.	Region	Dose (mg)	Product	Subjects	Matrix	C_{max} (ng/ml)	C_{max} (ng/ml) [adjusted to 200 mg]	AUC (ng h/ml)	AUC (ng h/ml) [adjusted to 200 mg]	T_{max} (hours)	Conditions	Comments	Included in pooled analysis
[48]	IE	100	Mexitil Capsules (Boehringer)	12	Plasma	177	354.0	2511	5022.0	1.9	Fasting	Healthy subjects	YES
		200		12		381	381.0	5094	5094.0	1.8			
		300		12		560	373.3	6870	4580.0	2			
		400		12		885	442.5	11373	5686.5	2.6			
		600		11		1223	407.7	16438	5479.3	1.8			
[39]	DE	400	Mexiletine Capsules	6	Plasma	770	385.0	7707	3853.5	2.16	Fasting	Healthy subjects	YES
[215]	DE	400	Mexitil Capsules (Boehringer)	10	Plasma	1920	960.0	25820	12910.0	1.7	Fasting	Healthy subjects before administration of antacid	YES
[52]	CA	200	Mexitil Capsules (Boehringer)	7	Blood	-	-	-	-	-	Fasting	Healthy subjects	YES
[195]	AU	400	Mexiletine Capsules	6	Plasma	1000	500.0	17670	8835.0	1.7	Fasting	Healthy subjects, before administration of phenytoin	YES
[90]	FI	400	Mexitil Capsules (Boehringer)	7	Plasma	650	325.0	10870	5435.0	4.68	Fasting	Study I: patients with acute myocardial infarction in the acute phase	YES
				7		1080	540.0	13230	6615.0	1.46		Study II: patients with acute myocardial infarction in the recovery phase	
[78]	CA	100	Mexitil Capsules (Boehringer)	15	Serum	177.4	354.8	NR	-	1.9	Fasting	7 elderly and 8 young healthy subjects	YES

2.5 Clinical overview

Ref.	Region	Dose (mg)	Product	Subjects	Matrix	C_{max} (ng/ml)	C_{max} (ng/ml) [adjusted to 200 mg]	AUC (ng h/ml)	AUC (ng h/ml) [adjusted to 200 mg]	T_{max} (hours)	Conditions	Comments	Included in pooled analysis
[216]	JP	200	Mexitil Capsules (Boehringer)	6	Serum	463	463.0	5520	5520.0	NR	Fasting	Healthy subjects, before administration of fluconazole	YES
[212]	JP	200	Mexitil Capsules (Boehringer)	9	Serum	438	438.0	6260	6260.0	NR	Fasting	Healthy Japanese subjects before administration of omeprazole	YES
[40]	IE	200	Mexiletine Capsules	5	Plasma	-	-	-	-	2	Fasting	Healthy subjects	YES
[217]	AU	400	Mexiletine Capsules	8	Plasma	1450	725.0	15770	7885.0	1.97	Fasting	Healthy subjects before administration of metoclopramide and atropine	YES
[57]	AU	200	Mexitil Capsules (Boehringer)	4	Plasma	-	-	-	-	-	Fasting	Healthy subjects	YES
		400		4		-	-	-	-	-			
[194]	FI	400	Mexitil Capsules (Boehringer)	8	Serum	1020	510.0	12530	6265	1.91	Fasting	Healthy subjects before administration of rifampicin	YES
[218]	CA	300	Mexiletine Capsules	6	Plasma	740	493.3	NR	-	1.13	Fasting	Healthy subjects before administration of cimetidine	NO
[219]	DE	100	Mexitil Capsules (Boehringer) and Mexiletine Tablets	6	Plasma	620	1240	5700	11400	1.42	Fasting	Healthy subjects before administration of cimetidine or ranitidine	NO
[58]	JP	50	Mexiletine Capsules	3	Plasma	110	440	1058	4232	2.9	NR	Patients with ventricular arrhythmias	YES
		100		3		190	380	2053	4106	2.77			
		150		5		410	546.7	5178	6904	3.09			
		200		6		560	560	6446	6446	3.01			
		300		10		1090	726.7	12853	8568.67	3.02			

2.5 Clinical overview

Ref.	Region	Dose (mg)	Product	Subjects	Matrix	C_{max} (ng/ml)	C_{max} (ng/ml) [adjusted to 200 mg]	AUC (ng h/ml)	AUC (ng h/ml) [adjusted to 200 mg]	T_{max} (hours)	Conditions	Comments	Included in pooled analysis
[211]	JP	200	Mexiletine Capsules	6	Serum	536	536	5710	5710	2.17	Fasting	Healthy Japanese subjects before administration of fluvoxamine	YES
[220]	UK	200	Mexiletine Capsules	12	Plasma	690	690	7400	7400	2	Fasting	Patients with symptomatic ventricular arrhythmias	NO
[221]	UK	600	Mexiletine Capsules	38	Plasma	2200	733.3	NR	-	3	NR	Patients ventricular arrhythmias	NO
[222]	JP	400	Mexitil Capsules (Boehringer)	5	Serum	NR	-	NR	-	3	NR	Healthy Japanese subjects	YES
[85]	US	200	Mexiletine Capsules	14	Plasma	410	410	NR	-	3	Fasting	Subjects with renal failure (5 subjects required maintenance dialysis)	YES
[223]	US	100	Mexiletine Capsules	2	Serum	NR	-	NR	-	NR		Total 8 subjects (2 per dose group) with complex partial seizures	NO
		200		2		NR	-	NR	-	NR			
		300		2		NR	-	NR	-	NR			
		400		2		NR	-	NR	-	NR			
[77]	JP	200	Mexitil Capsules (Boehringer)	5	Plasma	470	470.0	5530	5530	NR	Fasting	Mean data from 5 subjects. CYP2D6*1/*1 data only	YES

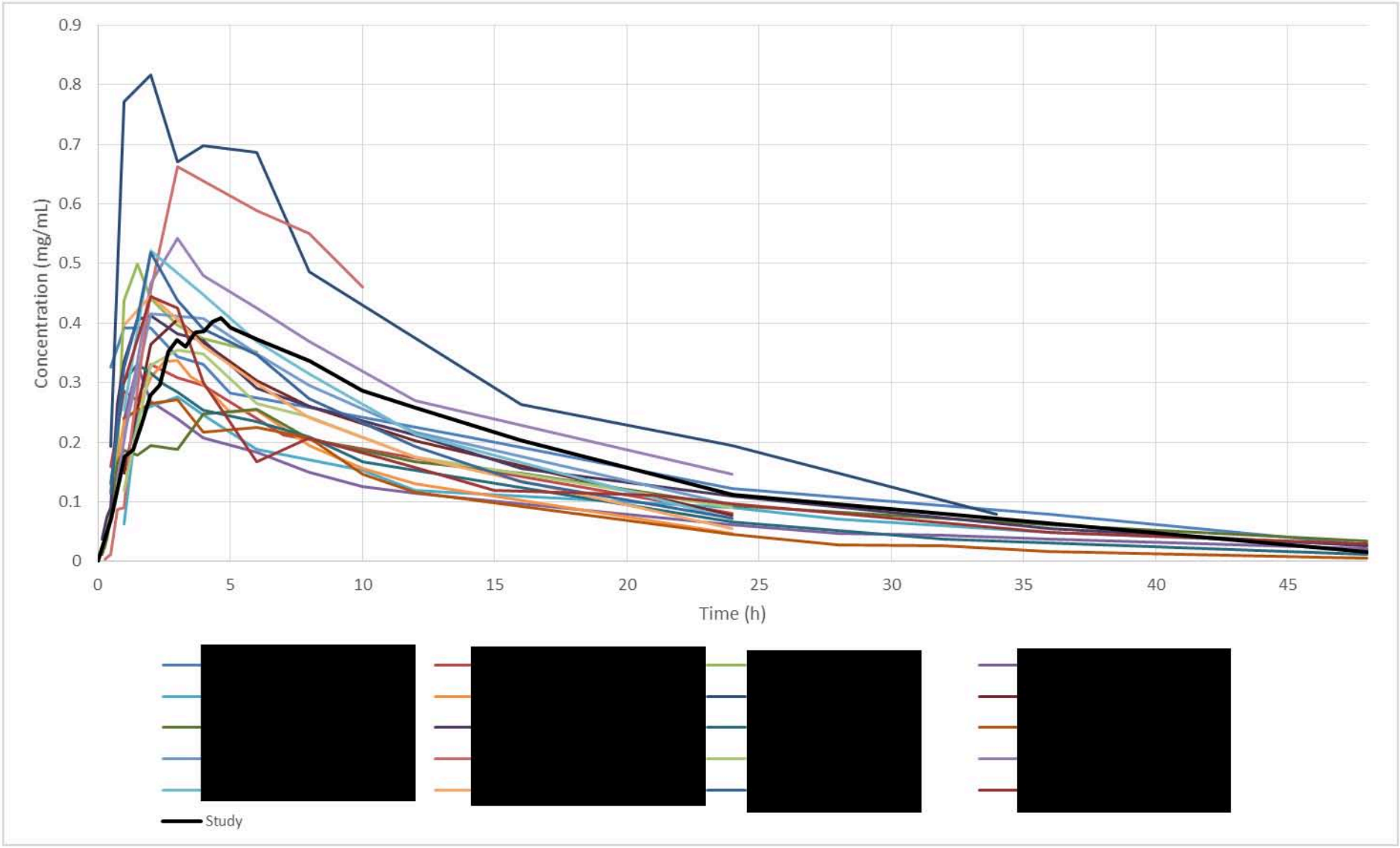


Figure 17 Concentration versus time profiles of mexiletine (literature data and study [redacted]

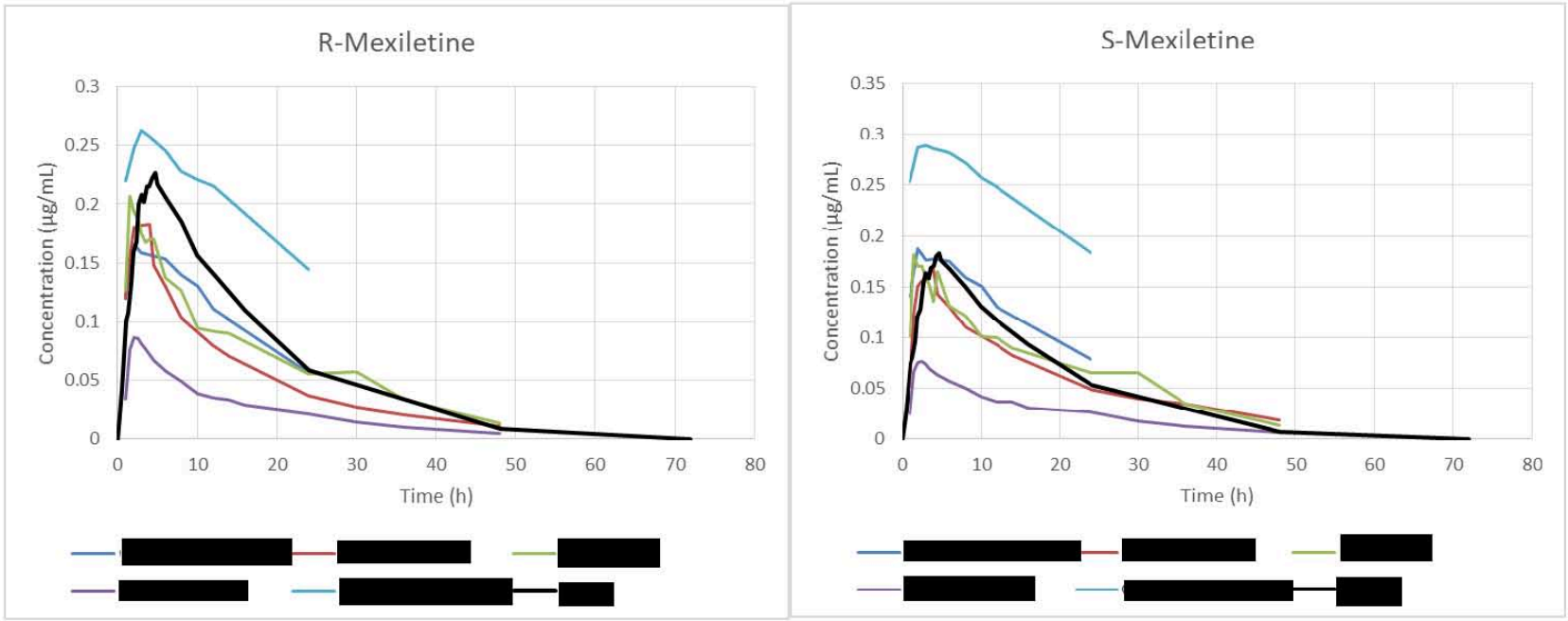


Figure 18 Concentration versus time profiles of R-Mexiletine (on the left) and S-Mexiletine (on the right) (literature data and study

2.5 Clinical overview

Table XXI Pharmacokinetic data for R- Mexiletine after oral administration (literature data)

Ref.	Region	Dose (mg)	Product	N	Matrix	C_{max} (ng/ml)	C_{max} (ng/ml) [adjusted to 200 mg]	AUC (ng h/ml)	AUC (ng h/ml) [adjusted to 200 mg]	T_{max} (hours)	Conditions	Comments	Included in pooled analysis
[53]	CA	300	Mexitil Capsules (Boehringer)	1	Plasma	NR	-	2040	1360	NR	Fasting	A healthy volunteer (100 kg)	YES
[46]	CA	300	Mexitil Capsules (Boehringer)	5	Plasma	285	190	3330	2220	2.1	Fasting	Healthy subjects	YES
[47]	CA	200	Mexitil Capsules (Boehringer)	12	Total serum	217	217	2800	2800	2.1	Fasting	Healthy subjects	YES
[26]	US	200	Mexitil Capsules (Boehringer)	6	Serum	NR	-	1370	1370	NR	Fasting	Healthy subjects	YES
[28]	CA	200	Mexiletine enantiomers (Boehringer)	1	Plasma	NR	-	NR	-	NR	NR	1 healthy subject	YES

Table XXII Pharmacokinetic data for S- Mexiletine after oral administration (literature data)

Ref.	Region	Dose (mg)	Product	N	Matrix	C_{max} (ng/ml)	C_{max} (ng/ml) [adjusted to 200 mg]	AUC (ng h/ml)	AUC (ng h/ml) [adjusted to 200 mg]	T_{max} (hours)	Conditions	Comments	Included in pooled analysis
[53]	CA	300	Mexitil Capsules (Boehringer)	1	Plasma	NR	-	2240	1493	NR	Fasting	A healthy volunteer (100 kg)	YES
[46]	CA	300	Mexitil Capsules (Boehringer)	5	Plasma	235	157	3570	2380	2.3	Fasting	Healthy subjects	YES
[47]	CA	200	Mexitil Capsules (Boehringer)	12	Total serum	196	196	2600	2600	2.3	Fasting	Healthy subjects	YES
[26]	US	200	Mexitil Capsules (Boehringer)	6	Serum	NR	-	1760	1760	NR	Fasting	Healthy subjects	YES
[28]	CA	200	Mexiletine enantiomers (Boehringer)	1	Plasma	NR	-	NR	-	NR	NR	1 healthy subject	YES

2.5.6.5.2 Comparison with other Mexiletine approved products

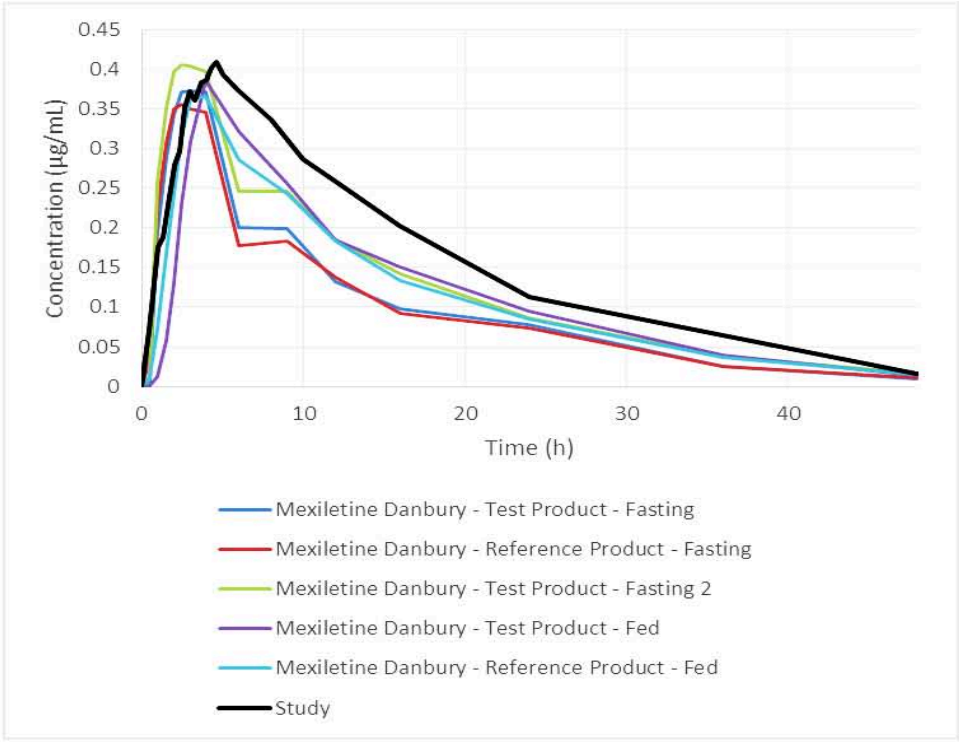
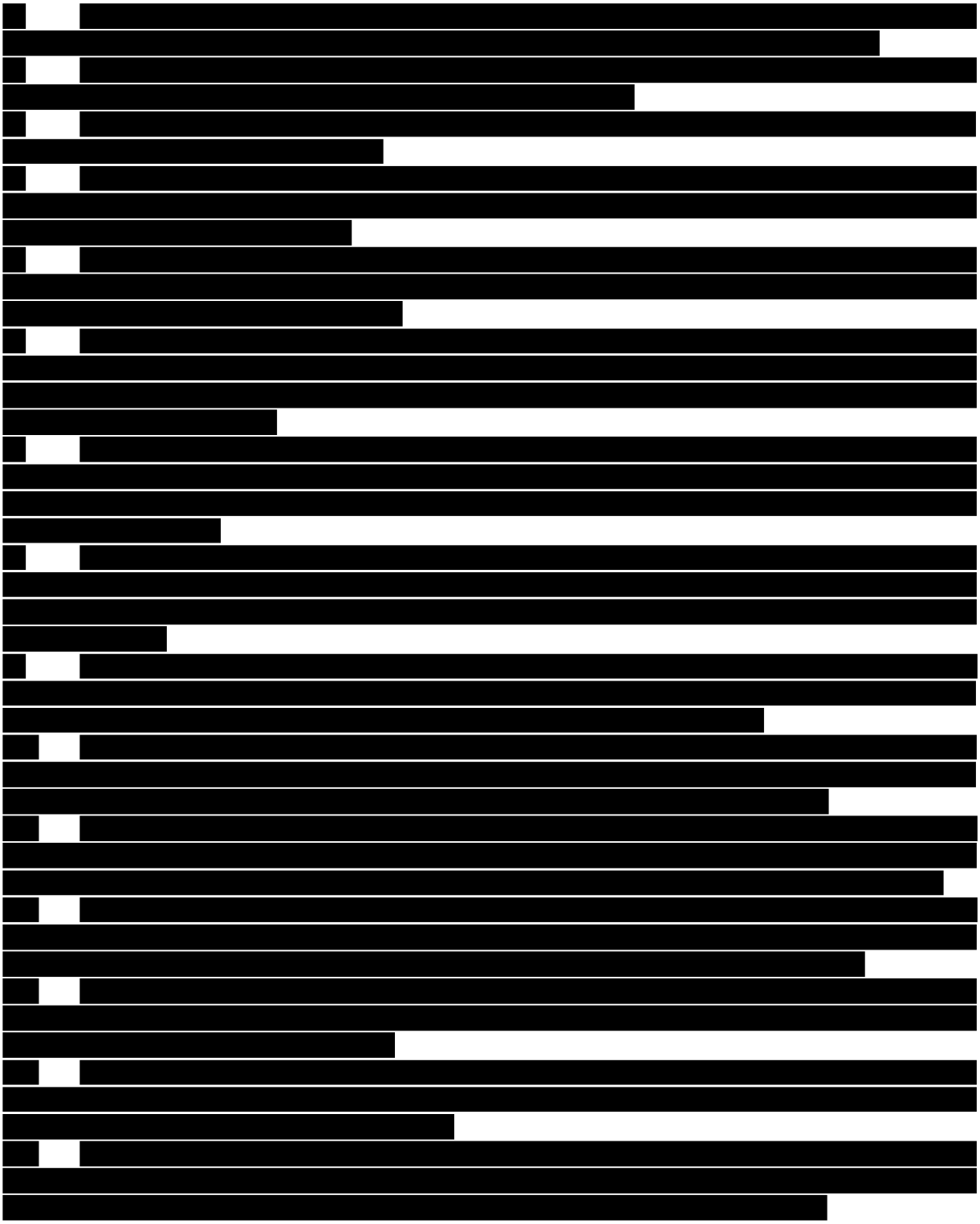
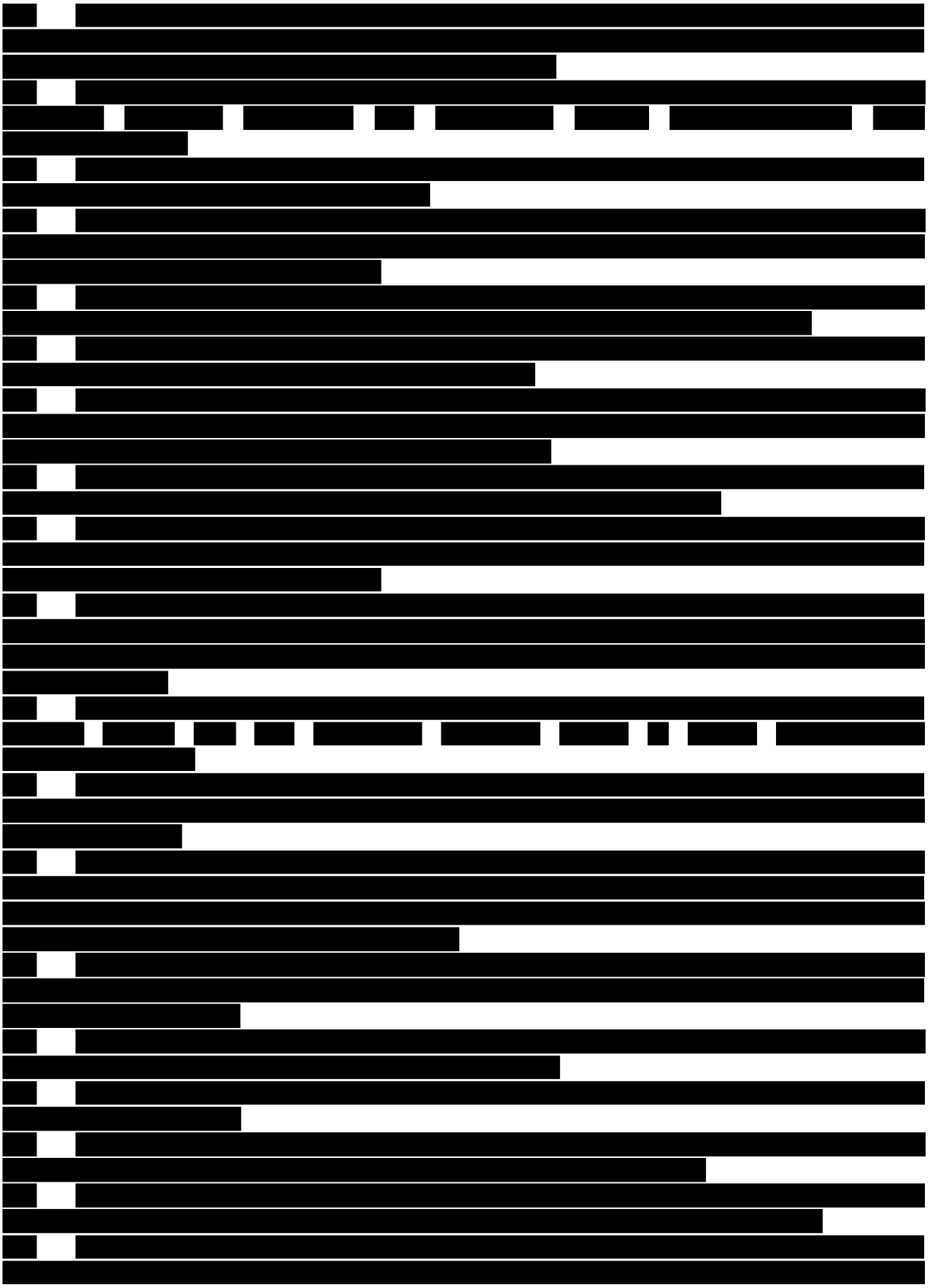
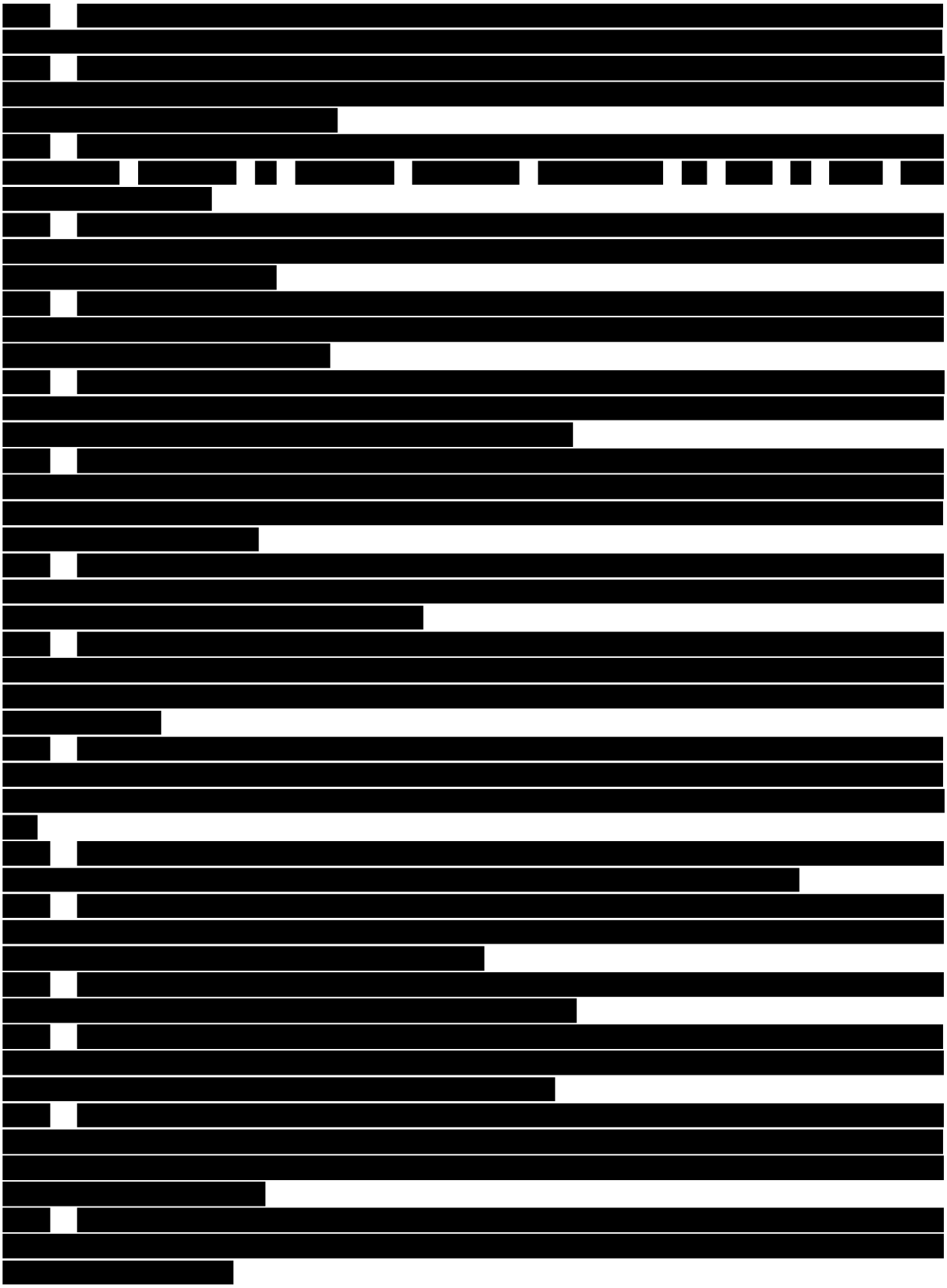


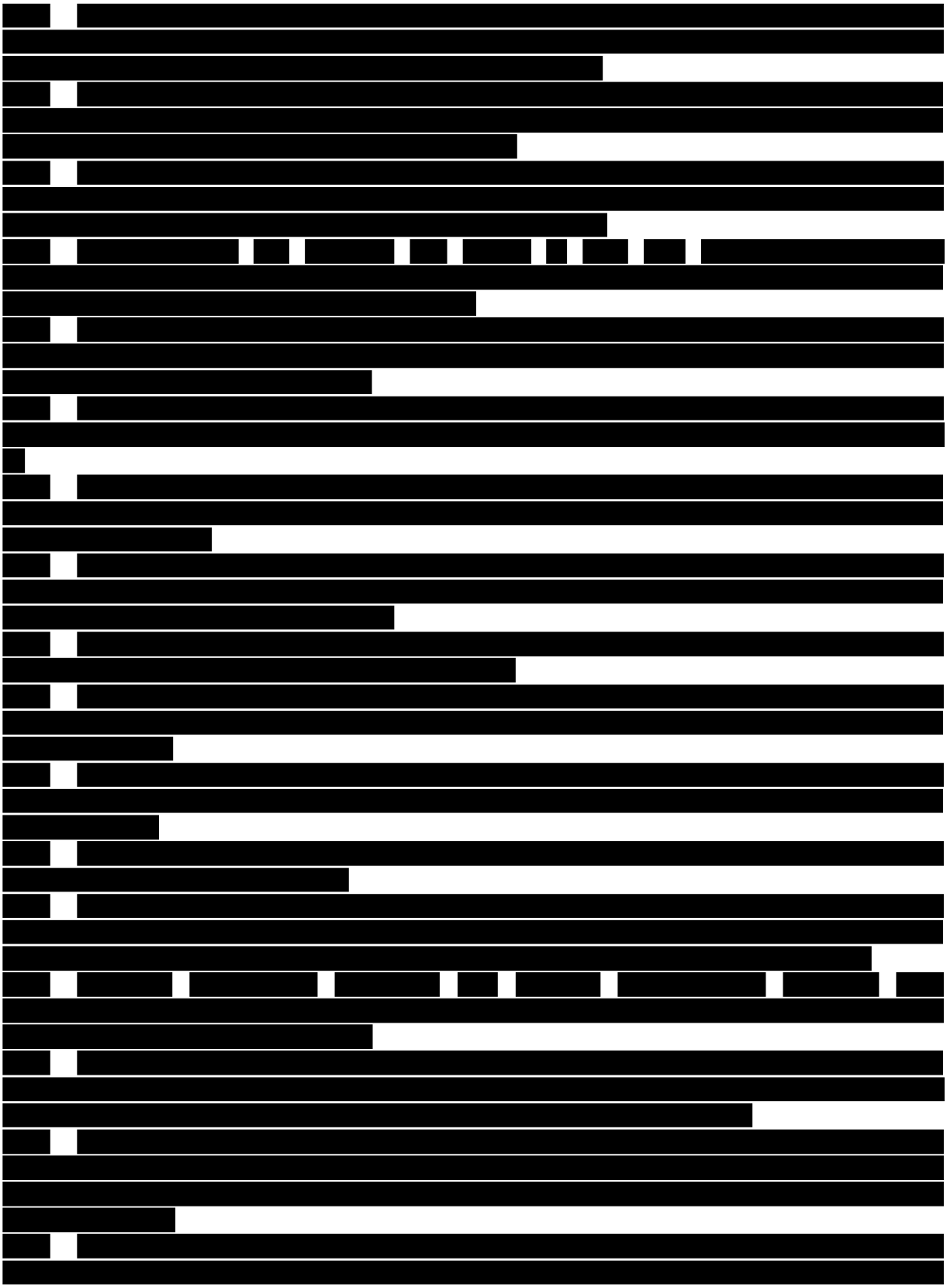
Figure 19 Concentration versus time profiles of Mexiletine (studies reported in the PARs of licensed products and study for the proposed product)

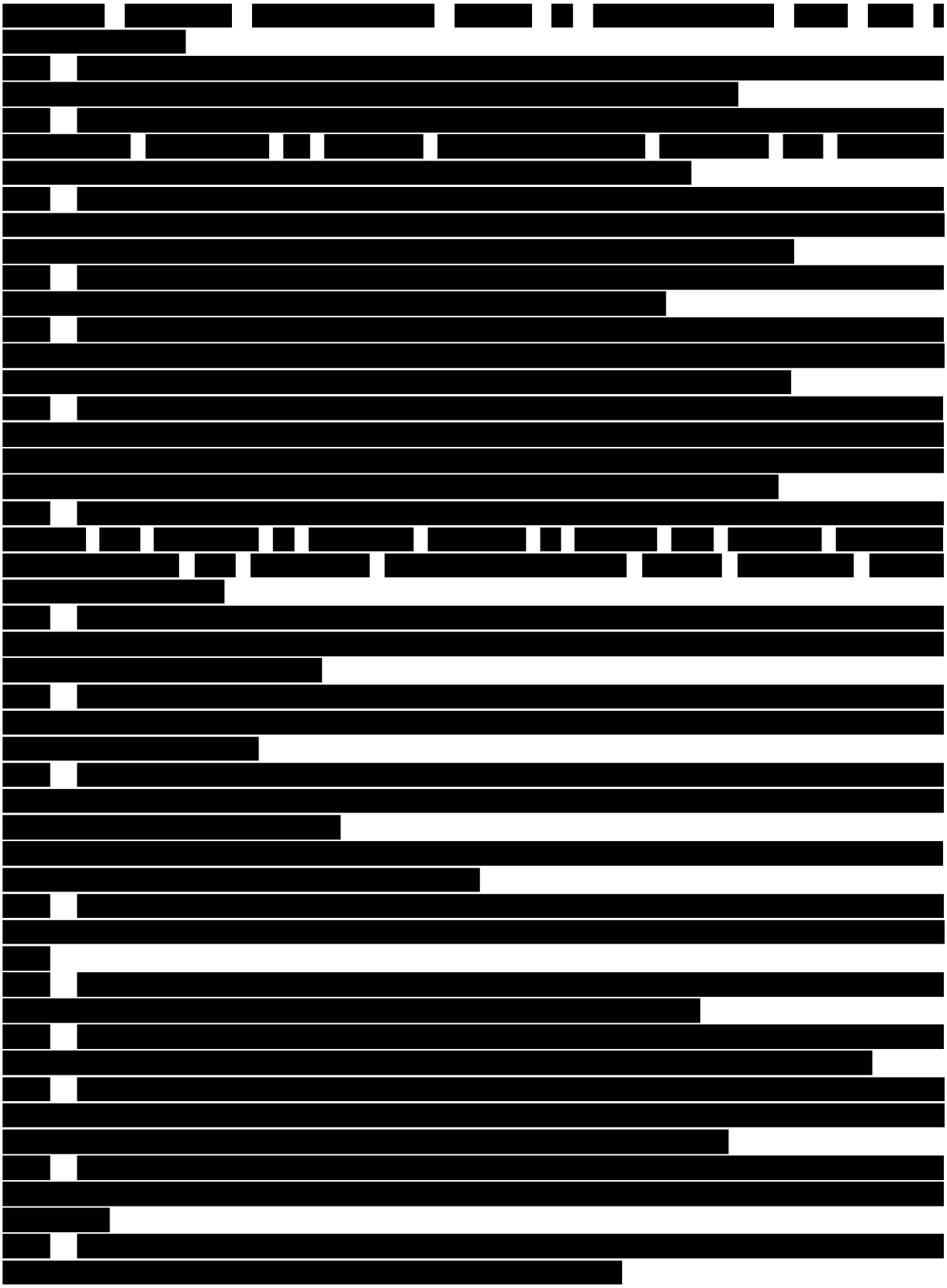
2.5.7 LITERATURE REFERENCES

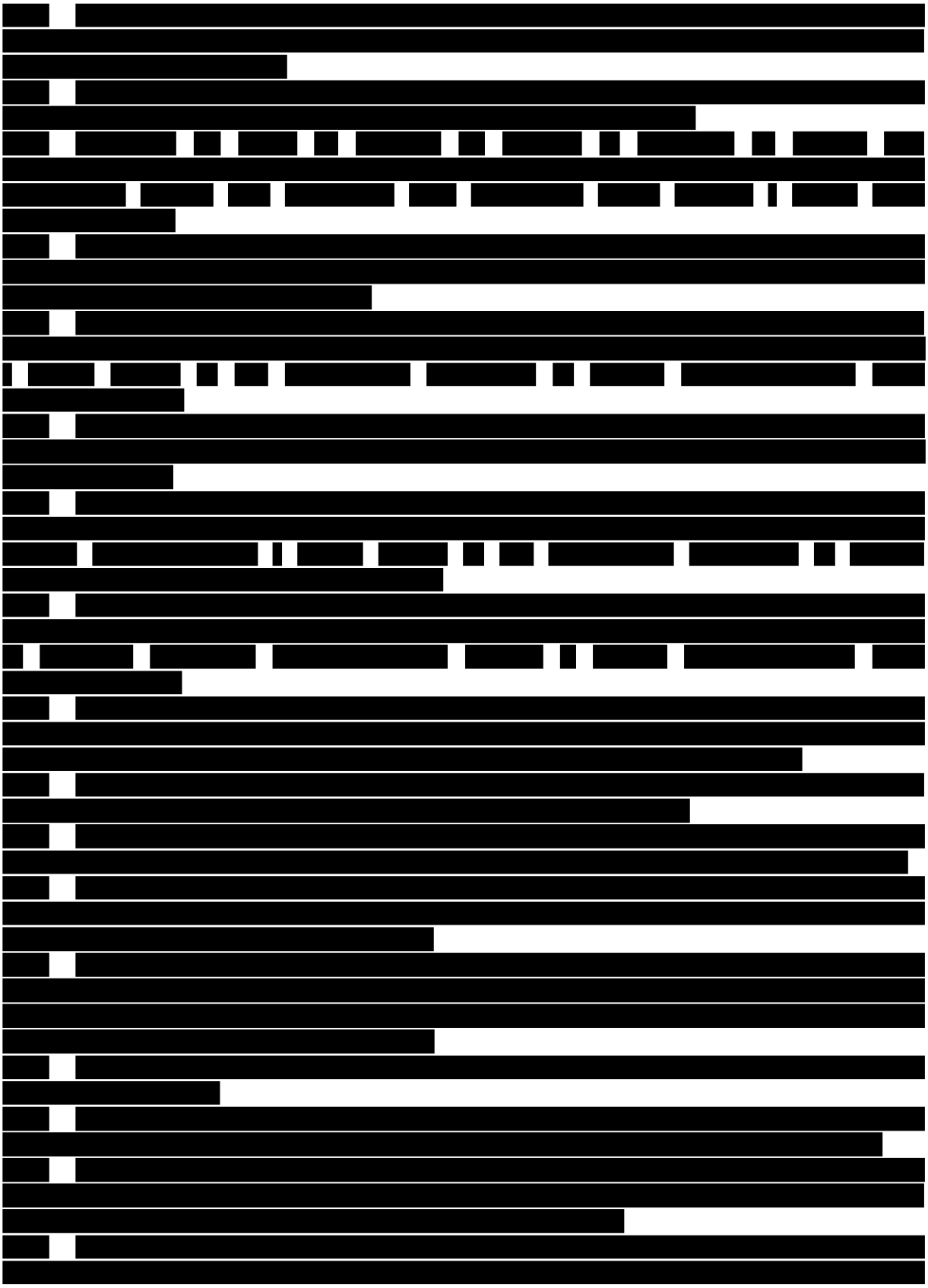












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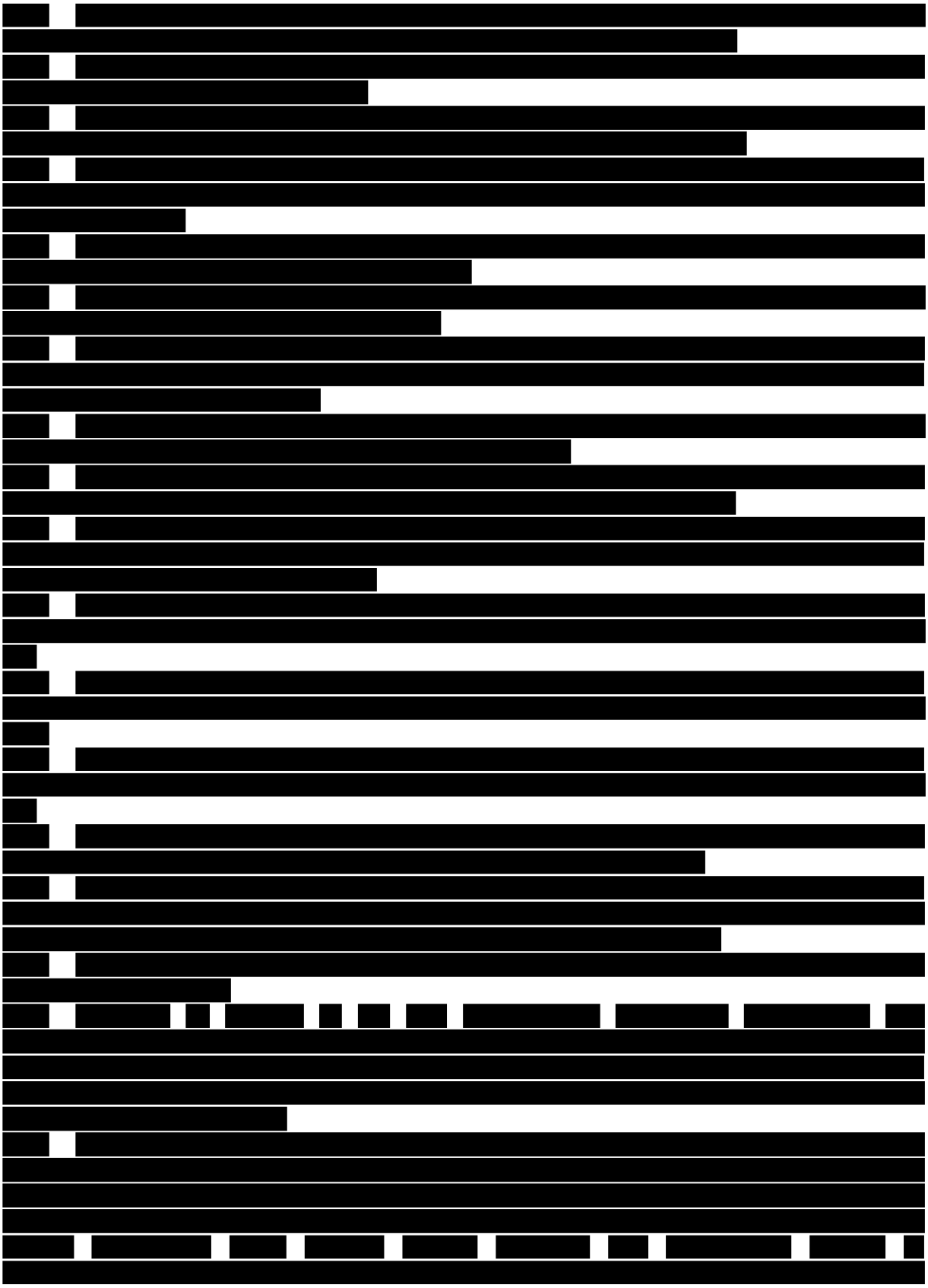

2.5 Clinical overview