Risk Management Plan (RMP)

EU Risk Management Plan for Mexiletine hydrochloride

RMP version to be assessed as part of this application:

RMP Version number:	0.3
Data lock point for this RMP:	[redacted]
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Rationale for submitting an updated RMP:	Updated RMP during marketing authorisation application procedure.
Summary of significant changes in this RMP:	• SmPC and PIL updated

QPPV name:	[redacted]
QPPV signature:	[redacted]

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PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Mexiletine hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	Cardiac therapy, antiarrhythmics, class Ib (C01BB02)
Marketing Authorisation Applicant	[redacted]
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	Mexiletine hydrochloride 50 mg Hard Capsules Mexiletine hydrochloride 100 mg Hard Capsules Mexiletine hydrochloride 200 mg Hard Capsules
Marketing authorisation procedure	National, UK
Brief description of the product	Chemical class Mexiletine is a non-selective voltage-gated sodium channel blocker which belongs to the Class IB anti-arrhythmic group of medicines. It is an aromatic ether and a primary amino compound.
	Summary of mode of action Mexiletine is a local anaesthetic, antiarrhythmic agent, structurally similar to lidocaine. Mexiletine is effective in the suppression of induced ventricular arrhythmias. Mexiletine, like lidocaine inhibits the inward sodium current, thus reducing the rate of rise of the action potential, Phase 0. Mexiletine decreases the effective refractory period (ERP) in Purkinje fibers. The decrease in ERP is of lesser magnitude than the decrease in action potential duration (APD), with a resulting increase in the ERP/APD ratio.
	Important information about its composition Chemically active substance
Hyperlink to the Product Information	Hyperlink to SmPC Hyperlink to PIL
Indication(s) in the EEA	Current (if applicable): Not applicable
	Proposed (if applicable): Mexiletine is indicated for the treatment of documented ventricular arrhythmias which, in the judgement of the physician, are considered as life-threatening. Class I antiarrhythmic drugs have not been shown to improve survival in patients with ventricular arrhythmias.
Dosage in the EEA	Current (if applicable): Not applicable
	Proposed (if applicable): Posology Treatment with mexiletine should be initiated and monitored by a specialist experienced in the treatment of cardiac arrhythmias. The optimal dosage should be determined individually based on the patient's response and tolerance. *Adults*

	In patients in whom rapid control of ventricular arrhythmia is needed, a loading dose of 400 mg may be given. A maintenance dose of 150 mg to 300 mg, two to three times daily is recommended. If necessary, dose may be adjusted in 50 or 100 mg increments. A minimum of two to three days between dose adjustments is recommended. Dosage should not exceed 1200 mg per day.
Pharmaceutical form(s) and strengths	Current (if applicable): Not applicable
	Proposed (if applicable): 50 mg, 100 mg, 200 mg Hard Capsules
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for "Well established medicinal use" medicinal products.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for "Well established medicinal use" medicinal products.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for "Well established medicinal use" medicinal products.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for "Well established medicinal use" medicinal products.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for "Well established medicinal use" medicinal products.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for "Well established medicinal use" medicinal products.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Potentiation of tremor in patients with Parkinson
- Insomnia, somnolence
- Headache, paraesthesia, vision blurred
- Speech disorders
- Diplopia, dysgeusia
- Vertigo
- Flushing, hypotension, hot flush
- Abdominal pain
- Nausea
- Diarrhoea, vomiting
- Acne

- Pain in the extremities
- Fatigue, asthenia, chest discomfort, malaise

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Hypersensitivity to the active substance, or to any of the excipients, hypersensitivity to any local anaesthetic
- Leukopenia, thrombocytopenia
- Lupus-like syndrome
- Hallucinations, confusional state
- Atrioventricular block
- Circulatory collapse
- Pulmonary fibrosis
- Oesophageal ulcers and perforation
- Hepatic function abnormal, drug-induced liver injury, liver disorder, hepatitis

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- None

Known risks that do not impact the risk-benefit profile:

- None

Other risks, which are considered not important:

- None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Severe cutaneous adverse reactions (SCARs)

Risk-benefit impact:

Drug reaction with eosinophilia and systemic symptoms (DRESS) refers to a syndrome which includes in its complete form severe cutaneous eruptions, fever, lymphadenopathy, hepatitis, haematological abnormalities with eosinophilia and atypical lymphocytes, and can involve other organs. Symptoms typically occur 1-8 weeks after exposure to the medicinal product. Severe systemic manifestations are responsible for a 10% mortality rate. Incidence of DRESS has been reported between 1:100 and 1:10.000 patients treated.

Several medicinal products including anticonvulsants, antibiotics and also mexiletine have been identified as possible causes. Patients with known hypersensitivity to mexiletine or any other ingredients of this product or to any local anaesthetic are at high risk of developing DRESS and should not receive mexiletine.

[redacted]

Important Identified Risk 2: Cardiac arrhythmia

Risk-benefit impact:

Mexiletine may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed.

Before starting mexiletine treatment, detailed and careful cardiac evaluation (ECG, 24-48-hour Holter-monitoring and echocardiography) should be carried out in all patients in order to determine the cardiac tolerability of mexiletine. A cardiac evaluation is recommended shortly after treatment start (e.g. within 48 hours).

Throughout treatment with mexiletine, and in relation with dose changes, detailed cardiac evaluation, including ECG, should be carried out before and after any dose increase. During maintenance treatment, detailed cardiac evaluation, including ECG, 24-48 hour Holter-monitoring and echocardiography, is recommended at least annually, or more frequently if considered necessary as part of routine cardiac assessment.

Patients should be informed about the presenting symptoms of arrhythmias (fainting, palpitation, chest pain, shortness of breath, light-headedness, lipothymia, and syncope) and should be advised to immediately contact an emergency centre if there are any symptoms of arrhythmias.

Tachycardia is also presented as a common adverse reaction and bradycardia as an uncommon adverse effect.

[redacted]

Important Identified Risk 3: Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine

Risk-benefit impact:

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) 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.

The CYP1A2 substrate blood levels should be monitored, particularly when the mexiletine dose is changed. An appropriate adjustment in the dose of the CYP1A2 substrate should be considered.

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.

[redacted]

Important Identified Risk 4: Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment

Risk-benefit impact:

Mexiletine is mainly (90%) metabolized in the liver, the primary pathway being CYP2D6 metabolism, although it is also a substrate for CYP1A2. Plasma elimination half-life may be prolonged in moderate

to severe hepatic disease. In severe hepatic impairment, total clearance is diminished, which can lead to considerable increase in plasma levels of mexiletine and associated risk of side effects of mexiletine. [1]

[redacted]

Important Potential Risk 1: Increased frequency of seizure episodes in patients with epilepsy

Risk-benefit impact:

Epileptic patients need to be monitored because mexiletine can increase the frequency of seizure episodes. Furthermore, seizure is an uncommon adverse reaction from Nervous system.

Since the current data do not suggest a strong connection between mexiletine and increased frequency of seizure episodes in patients with epilepsy, the risk has been classified as an important potential risk.

Important Potential Risk 2: Off-label use in children

Risk-benefit impact:

No specific information on the use of Mexiletine Hard Capsules in the children is available.

Since the safety and efficacy of mexiletine in children and adolescents aged 0 to 18 years, have not been established, the risk has been classified as an important potential risk.

Missing information 1: Effect on fertility and use in pregnancy

Risk-benefit impact:

There are no or limited amount of data from the use of mexiletine in pregnant women. Limited clinical data of the use of mexiletine in pregnant women shows that mexiletine crosses the placenta and reaches the foetus. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

As a precautionary measure, it is preferable to avoid the use of mexiletine during pregnancy.

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

Missing information 2: Safety in elderly

Risk-benefit impact:

No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

Missing information 3: Use in patients with severe renal impairment

Risk-benefit impact:

The experience with mexiletine in patients with severe renal impairment is limited. Therefore, the use of mexiletine is not recommended in this patient population. [2]

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; individual dose titration is advised in these conditions.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

This section is not applicable for an initial Marketing Authorisation Application.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk 1: Severe cutaneous adverse reactions (SCARs)

Potential mechanisms: Mexiletine Hard Capsules are contraindicated in patients with known hypersensitivity to mexiletine, or to any of the excipients or to any local anaesthetic as there is possibility of occurrence of potentially severe cutaneous eruptions, fever, lymphadenopathy, hepatitis, haematological abnormalities with eosinophilia and atypical lymphocytes, and can involve other organs.

The mechanism for the immunogenicity is not clear, although a role of reactive drug metabolites in initiating an immune response via hapten formation has been suggested [(3)].

Evidence source(s) and strength of evidence: Severe cutaneous adverse reactions (SCARs) are an identified risk of mexiletine. Severe cutaneous adverse reactions (SCARs) are a listed risk in the RMP of Mexiletine product (Namuscla). [(1)]

Characterisation of the risk: This is a risk of high severity, since there is possibility of occurrence of potentially severe cutaneous eruptions, fever, lymphadenopathy, hepatitis, haematological abnormalities with eosinophilia and atypical lymphocytes, and can involve other organs. The expected incidence rate of drug reaction with eosinophilia and systemic symptoms is < 1/10,000 (classified as a very rare adverse reaction). The incidence rate of Stevens-Johnson syndrome and dermatitis exfoliative (classified as a not known frequency adverse reaction) cannot be estimated from the available data.

Risk factors and risk groups: Patients with known hypersensitivity to mexiletine, or to any of the excipients or to any local anaesthetic.

Preventability: The risk is minimised by providing supportive information to the prescriber and the patient about the potential severe cutaneous adverse reactions.

Impact on the risk-benefit balance of the product: Mexiletine Hard Capsules are indicated for the treatment of ventricular arrhythmias, which are considered as life threatening by the physician. Patients with known hypersensitivity to mexiletine or of the excipients or to any local anaesthetic are at high risk of developing severe cutaneous adverse reactions and for this reason, mexiletine-including medicinal products are contraindicated to them.

Public health impact: Considering the high number and severity of the reported Serious Cutaneous Adverse Reaction (SCAR) Stevens-Johnson syndrome (i.e. 34 reported cases as stated within the PSUR covering the period 2005-2008), the RMP has included the term 'Severe Cutaneous Adverse Reactions' (SCARs), which include DRESS and Stevens-Johnson syndrome, as an Important Identified Risk. [(4)]

Important Identified Risk 2: Cardiac arrhythmia

Potential mechanisms: Mexiletine is a class I b antiarrhythmic drug according to the Vaughan Williams classification and as such, it may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed. Mexiletine can cause adverse effects that are directly linked to blockade of sodium channels and among these adverse effects, cardiovascular problems, especially proarrhythmia defined as either the onset of a new arrhythmia or the aggravation of a pre-existing arrhythmia.

A continuously rising number of cardiac and non-cardiac agents have been implicated in proarrhythmia and SCD (sudden cardiac death). Abnormalities in repolarization and/or depolarization of cardiac cells through changes in ion channels and myocardial zones are the main pathophysiological mechanisms manifested as long QT, short QT and BS in routine clinical practice. Mexiletine is included in the drugs implicated in QT interval prolongation and torsades de pointes. [5]

Evidence source(s) and strength of evidence: Cardiac arrhythmia is an identified risk of mexiletine. It has been identified in the literature in a number of patients. Mexiletine is a class I b antiarrhythmic drug according to the Vaughan Williams classification, and as such, it may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed.

Characterisation of the risk: This is a risk of high severity, since one of the most serious reported adverse reactions in patients treated with mexiletine is arrhythmia (atrioventricular block, arrhythmia, ventricular fibrillation). The expected incidence rate of tachycardia is ≥ 1/100 to < 1/10 (classified as a common adverse reaction). Bradycardia has been classified as an uncommon adverse reaction with an incidence rate ≥ 1/1,000 to < 1/100. The incidence rate of atrioventricular block is not known.

Risk factors and risk groups: Mexiletine should be administered with caution in patients with pre-existing cardiac conduction anomalies. The advent (under mexiletine therapy) of an atrioventricular block, a permanent complete heart block, or a sinoatrial block necessitates the interruption of the mexiletine treatment. The concomitant use of mexiletine and antiarrhythmic drug inducing torsades de pointes increases the risk of potentially lethal torsades de pointes. Coadministration of hepatic enzymes (CYP1A2 and CYP2D6) inhibitors (such as ciprofloxacin, fluvoxamine, propafenone or quinidine) may significantly increase mexiletine exposure and thus the associated risk of side effects of mexiletine.

Preventability: The risk is minimised by providing supportive information to the prescriber and the patient about the potential risk of cardiac arrhythmia.

Impact on the risk-benefit balance of the product: The safety profile of mexiletine in the antiarrhythmic indications is well-established. The most important safety issue is that mexiletine can trigger arrhythmia or aggravate an existing arrhythmia, whether or not it has been diagnosed. [4]

Public health impact: The expected incidence rate of tachycardia is between ≥ 1/100 to < 1/10 patients (classified as a common adverse reaction). The expected incidence rate of bradycardia is between ≥ 1/1,000 to < 1/100 patients (classified as an uncommon adverse reaction).

Important Identified Risk 3: Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine

Potential mechanisms: Mexiletine is a potent inhibitor of CYP1A2. Therefore, co-administration of mexiletine with a medicinal product metabolised by CYP1A2 (such as theophylline, caffeine or tizanidine) may be associated with elevations in plasma concentrations of the concomitant medicine that could increase or prolong the therapeutic efficacy and/or adverse events, especially if mexiletine is co-administered with CYP1A2 substrate with narrow therapeutic window.

Interactions between theophylline and mexiletine are mostly explained by inhibition of theophylline metabolism because of competitive inhibition of CYP1A2 by mexiletine. [9-11]

Evidence source(s) and strength of evidence: Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine is an identified risk of mexiletine with a good understanding of the underlying mechanism.

Characterisation of the risk: This is a moderate severe risk. Concurrent administration of mexiletine may increase plasma levels of theophylline and caffeine.

Risk factors and risk groups: Patients that mexiletine is co-administered with CYP1A2 substrate with narrow therapeutic window.

Preventability: The risk is minimised by providing supportive information to the prescriber and the patient about the potential risk of toxicity of CYP1A2 substrates with narrow therapeutic window. During the treatment with mexiletine patient might require treatment with other concomitant medications and they can inform their healthcare professionals about ongoing treatment with mexiletine before starting any other medication.

The CYP1A2 substrate blood levels should be monitored, particularly when the mexiletine dose is changed. An appropriate adjustment in the dose of the CYP1A2 substrate should be considered.

Impact on the risk-benefit balance of the product: Data indicate that the co-administration of caffeine, a substrate of CYP1A2, does not lead to clinically significant changes in mexiletine plasma concentrations. However, increased plasma concentrations of caffeine caused by the co-administration of mexiletine may still be of concern in patients presenting with cardiac arrhythmias. (6)

Public health impact: Not known.

Important Identified Risk 4: Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment

Potential mechanisms: Mexiletine is mainly (90%) metabolized in the liver, the primary pathway being CYP2D6 metabolism, although it is also a substrate for CYP1A2. Plasma elimination half-life may be prolonged in moderate to severe hepatic disease. In severe hepatic impairment, total clearance is diminished, which can lead to considerable increase in plasma levels of mexiletine and associated risk of side effects of mexiletine.

Hepatic dysfunction might be expected to affect mexiletine pharmacokinetics, and indeed it was found a decreased plasma clearance of mexiletine in patients with cirrhosis. (8)

Evidence source(s) and strength of evidence: Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment, is an identified risk of mexiletine with a good understanding of the underlying mechanism.

Characterisation of the risk: This is a severe risk, which can lead to considerable increase in plasma levels of Mexiletine and associated risk of side effects of mexiletine.

Risk factors and risk groups: Plasma elimination half-life may be prolonged in moderate to severe hepatic disease, individual dose titration is advised in this condition.

The experience with mexiletine in patients with severe hepatic impairment is limited. Therefore, mexiletine should not be used in this patient population.

Preventability: Individual dose titration is advised in moderate to severe hepatic disease.

The experience with mexiletine in patients with severe hepatic impairment is limited. Therefore, mexiletine should not be used in this patient population.

Monitoring is particularly recommended in the following situation: hepatic failure.

Impact on the risk-benefit balance of the product: Mexiletine Hard Capsules are indicated for the treatment of ventricular arrhythmias, which are considered as life threatening by the physician. The actual impact on treatment of ventricular arrhythmias is major.

Plasma elimination half-life may be prolonged in moderate to severe hepatic disease and in severe hepatic impairment, total clearance is diminished, which can lead to considerable increase in plasma levels of mexiletine and associated risk of side effects of mexiletine.

Public health impact: Not known.

Important Potential Risk 1: Increased frequency of seizure episodes in patients with epilepsy

Potential mechanisms: Common elements of pathogenesis create a basis for the assumption that antiarrhythmic drugs (AADs) may affect seizure phenomena and interact with antiepileptic drugs (AEDs). It is well known that several AEDs present antiarrhythmic activity. On the other hand, some AADs may have anticonvulsant properties or sometimes biphasic action on seizures. Particularly AEDs blocking Na+, K+ and/or Ca2+ channels may affect cardiac conduction and central autonomic control in susceptible patients. Nevertheless, several case reports illustrate arrhythmogenic effect of some AEDs. [7]

Evidence source(s) and strength of evidence: Common elements of pathogenesis create a basis for the assumption that antiarrhythmic drugs (AADs) may affect seizure phenomena and interact with antiepileptic drugs (AEDs).

Characterisation of the risk: Since the current data do not suggest a strong connection between mexiletine and increased frequency of seizure episodes in patients with epilepsy, the risk has been classified as an important potential risk.

Risk factors and risk groups: Patients with known history of epilepsy and on antiepileptic drugs (AEDs).

Preventability: The risk of increased frequency of seizure episodes in patients with epilepsy has been included in the information provided to prescribers and patients. Epileptic patients need to be monitored because mexiletine can increase the frequency of seizure episodes.

Impact on the risk-benefit balance of the product: The impact is moderate. Epileptic patients need to be monitored because mexiletine can increase the frequency of seizure episodes.

Public health impact: The expected incidence rate of seizure episodes is between ≥ 1/1,000 to < 1/100 patients (classified as an uncommon adverse reaction).

Important Potential Risk 2: Off-label use in children

Potential mechanisms: Ventricular arrhythmias may occur at all ages, including childhood and adolescence. Therefore, the possibility of off-label use in the paediatric population cannot be excluded.

Evidence source(s) and strength of evidence: No specific information on the use of this product in the children is available.

Characterisation of the risk: The possibility of off-label use in children cannot be excluded.

Risk factors and risk groups: Children with ventricular arrhythmias, which are considered as life threatening by the physician.

Preventability: It has been included in the information provided to prescribers and patients that “no specific information on the use of this product in the children is available”. The indication of Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules is clearly stated in the information provided to prescribers and patients.

Impact on the risk-benefit balance of the product: Unknown.

Public health impact: Unknown.

SVII.3.2. Presentation of the missing information

Missing information 1: Effect on fertility and use in pregnancy

Evidence source: There are no or limited amount of data from the use of mexiletine in pregnant women. Limited clinical data of the use of mexiletine in pregnant women shows that mexiletine

crosses the placenta and reaches the foetus. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

As a precautionary measure, it is preferable to avoid the use of mexiletine during pregnancy.

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

Population in need of further characterisation: Pregnant women and women that are planning to have a baby.

Missing information 2: Safety in elderly

Evidence source: Experience with mexiletine in patients aged > 65 years is limited.

Population in need of further characterisation: Elderly.

Missing information 3: Use in patients with severe renal impairment

Evidence source: The experience with mexiletine in patients with severe renal impairment is limited. Therefore, the use of mexiletine is not recommended in this patient population.

Population in need of further characterisation: Patients with severe renal impairment.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	1. Severe cutaneous adverse reactions (SCARs) 2. Cardiac arrhythmia 3. Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine 4. Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment
Important potential risks	1. Increased frequency of seizure episodes in patients with epilepsy 2. Off-label use in children
Missing information	1. Effect on fertility and use in pregnancy 2. Safety in elderly 3. Use in patients with severe renal impairment

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for patients who experience cardiac arrhythmia:

A targeted follow-up questionnaire will be used, to monitor and further characterise the risk of cardiac arrhythmia. A specific questionnaire will be completed by the patient's doctor, to obtain structured information on reported suspected adverse reaction of cardiac arrhythmia. The completed questionnaires will help the marketing authorisation holder to collect additional data on the safety concern of cardiac arrhythmia.

The adverse reaction follow-up form is presented in Annex 4 of the RMP.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

This section is not applicable. There are no additional pharmacovigilance activities such as non-clinical, clinical or epidemiological (non-interventional or interventional) studies.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

This section is not applicable. There are no additional pharmacovigilance activities such as non-clinical, clinical or epidemiological (non-interventional or interventional) studies.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This section is not applicable. There are no planned and on-going imposed post-authorisation efficacy studies.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to other medicinal products containing mexiletine.

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Severe cutaneous adverse reactions (SCARs)	Routine risk communication: • SmPC section 4.3, 4.4 and 4.8. • PL section 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - How to detect early signs and symptoms of severe cutaneous adverse reactions presented in PL section 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

Cardiac arrhythmia	Routine risk communication: • SmPC section 4.1, 4.3, 4.4 and 4.8. • PL section 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - Evaluation before treatment start in order to determine if the documented ventricular arrhythmias are considered as life-threatening by the physician, stated in SmPC section 4.1. - Recommendation for initiation of treatment and monitoring by a specialist experienced in the treatment of cardiac arrhythmias, is stated in SmPC section 4.2. - Recommendation for healthcare professionals to determine the optimal dosage individually based on patient's response and tolerance is stated in SmPC section 4.2. - Recommendation for cautious use of Mexiletine in patients with hypotension or congestive heart failure because of its potential for depressing myocardial contractility is stated in SmPC section 4.4. - Recommendation for continuously monitoring in patients with second- or third-degree AV block if a ventricular pacemaker is operative, is stated in SmPC section 4.4. - Recommendation for caution when mexiletine is used in patients with first degree AV block or intraventricular conduction abnormalities is stated in SmPC section 4.4. - How patients can detect signs and symptoms of cardiac arrhythmia and when to contact an emergency centre immediately presented in PL section 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine	Routine risk communication: • SmPC section 4.5. • PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: - Recommendation for monitoring the CYP1A2 substrate blood levels presented in section 4.5 of SmPC. - Recommendation to patients to reduce their caffeine intake by half while on treatment with mexiletine stated in section 2 of the PIL. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment	Routine risk communication: • SmPC section 4.2 and 4.4. • PL section 2 and 3. Routine risk minimisation activities recommending specific clinical measures to address the risk: - Recommendation for initiation of treatment and monitoring by a specialist experienced in the treatment of cardiac arrhythmias, stated in SmPC section 4.2. - Recommendation for healthcare professionals to determine the optimal dosage individually based on patient's response and tolerance is stated in SmPC section 4.2. - Recommendation for careful evaluation in patients in whom an abnormal liver test has occurred, or who have signs or symptoms suggesting liver dysfunction. If persistent or worsening elevation of hepatic enzymes is detected, considerations should be given to discontinuing therapy. Stated in section 4.4 of SmPC. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

Increased frequency of seizure episodes in patients with epilepsy	Routine risk communication: • SmPC section 4.4 and 4.8. • PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: - Recommendation for use with caution in patients with history of seizures. Stated in section 4.4 of SmPC. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Off-label use in children	Routine risk communication: • SmPC section 4.2 and 5.1. • PL section 2 and 3. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Effect on fertility and use in pregnancy	Routine risk communication: • SmPC section 4.6. • PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

Safety in elderly	Routine risk communication: • SmPC section 4.2. • PIL section 3. Routine risk minimisation activities recommending specific clinical measures to address the risk: - Treatment with mexiletine should be initiated and monitored by a specialist experienced in the treatment of cardiac arrhythmias. The optimal dosage should be determined individually based on the patient's response and tolerance. Stated in section 4.2 of SmPC. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Use in patients with severe renal impairment	Routine risk communication: • SmPC section 4.2. • PIL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: - Recommendation to avoid the use of mexiletine in patients with creatinine clearance <30 ml/min, stated in SmPC section 4.2. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

V.2. Additional Risk Minimisation Measures

Additional risk minimisation 1

Healthcare Professional and Patient/Carer Guide

Objectives:

To ensure the safe and effective use of Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules and manage the risk of cardiac arrhythmia and the risk of adverse reactions in people with reduced mexiletine clearance due to hepatic dysfunction.

Rationale for the additional risk minimisation activity:

The guide aims to educate healthcare professionals (HCPs) to perform cardiac screening procedures in all patients before Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules initiation and to exclude those at greater risk of developing cardiac arrhythmias.

The guide aims to support HCPs to be cautious with dosing of patients with hepatic dysfunction and exclude patients with hepatic impairment to reduce the risk of adverse reactions due to reduced mexiletine clearance in those patients.

Target audience and planned distribution path:

Target audience:

Cardiologists, Anaesthesiologists, Intensive Care Unit Physicians.

Distribution to healthcare professionals.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Through adverse reactions reporting and signal detection.

Additional risk minimisation 2

Patient alert card

Objectives:

To prevent and/or minimise the important identified risk of cardiac arrhythmia in patients with ventricular arrhythmias.

Rationale for the additional risk minimisation activity:

Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules contain mexiletine and some patients taking mexiletine may develop cardiac arrhythmia which can be life-threatening. Patient alert card aims to raise awareness and inform healthcare providers and pharmacists about the ongoing medication and the risk of cardiac arrhythmia which can be life-threatening.

Target audience and planned distribution path:

Target audience: Patients receiving Mexiletine Hard Capsules.

Distribution path: Through healthcare professionals. Additionally, a copy of the Patient Alert Card will be included in each pack of medicine to ensure all patients receive it.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Through adverse reactions reporting and signal detection.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Severe cutaneous adverse reactions (SCARs)	Routine risk minimisation measures: • SmPC section 4.3, 4.4 and 4.8. • PL section 2 and 4. • How to detect early signs and symptoms of severe cutaneous adverse reactions presented in PL section 4. Additional risk minimisation measures: None	None Additional pharmacovigilance activities: None

Cardiac arrhythmia	Routine risk minimisation measures: • SmPC section 4.1, 4.3, 4.4 and 4.8. • PL section 2 and 4. • Evaluation before treatment start in order to determine if the documented ventricular arrhythmias are considered as life-threatening by the physician, stated in SmPC section 4.1. • Recommendation for initiation of treatment and monitoring by a specialist experienced in the treatment of cardiac arrhythmias is stated in SmPC section 4.2. • Recommendation for healthcare professionals to determine the optimal dosage individually based on patient's response and tolerance is stated in SmPC section 4.2. • Recommendation for cautious use of Mexiletine in patients with hypotension or congestive heart failure because of its potential for depressing myocardial contractility is stated in SmPC section 4.4. • Recommendation for continuously monitoring in patients with second- or third-degree AV block if a ventricular pacemaker is operative, is stated in SmPC section 4.4. • Recommendation for caution when mexiletine is used in patients with first degree AV block or intraventricular conduction abnormalities is stated in SmPC section 4.4. • How patients can detect signs and symptoms of cardiac arrhythmia and when to contact an emergency centre immediately presented in PL section 4. Additional risk minimisation measures: • Healthcare Professional and Patient/Carer Guide • Patient alert card	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: Targeted follow-up questionnaire, to monitor and further characterise the risk of cardiac arrhythmia. Additional pharmacovigilance activities: None

Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine	Routine risk minimisation measures: • SmPC section 4.5. • PL section 2. • Recommendation for monitoring the CYP1A2 substrate blood levels presented in section 4.5 of SmPC. • Recommendation to patients to reduce their caffeine intake by half while on treatment with mexiletine. Stated in section 2 of the PIL. Additional risk minimisation measures: None	None Additional pharmacovigilance activities: None
Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment	Routine risk minimisation measures: • SmPC section 4.2 and 4.4. • PL section 2 and 3. • Recommendation for initiation of treatment and monitoring by a specialist experienced in the treatment of cardiac arrhythmias, stated in SmPC section 4.2. • Recommendation for healthcare professionals to determine the optimal dosage individually based on patient's response and tolerance is stated in SmPC section 4.2. • Recommendation for careful evaluation in patients in whom an abnormal liver test has occurred, or who have signs or symptoms suggesting liver dysfunction. If persistent or worsening elevation of hepatic enzymes is detected, considerations should be given to discontinuing therapy. Stated in section 4.4 of SmPC. Additional risk minimisation measures: • Healthcare Professional and Patient/Carer Guide	None Additional pharmacovigilance activities: None
Increased frequency of seizure episodes in patients with epilepsy	Routine risk minimisation measures: • SmPC section 4.4 and 4.8. • PL section 2. • Recommendation for use with caution in patients with history of seizures. Stated in section 4.4 of SmPC. Additional risk minimisation measures: None	None Additional pharmacovigilance activities: None

Off-label use in children	Routine risk minimisation measures: • SmPC section 4.2 and 5.1. • PL section 2 and 3. Additional risk minimisation measures: None	None Additional pharmacovigilance activities: None
Effect on fertility and use in pregnancy	Routine risk minimisation measures: • SmPC section 4.6. • PL section 2. Additional risk minimisation measures: None	None Additional pharmacovigilance activities: None
Safety in elderly	Routine risk minimisation measures: • SmPC section 4.2. • PL section 3. • Recommendation for healthcare professionals: Treatment with mexiletine should be initiated and monitored by a specialist experienced in the treatment of cardiac arrhythmias. The optimal dosage should be determined individually based on the patient's response and tolerance. Stated in section 4.2 of SmPC. Additional risk minimisation measures: None	None Additional pharmacovigilance activities: None
Use in patients with severe renal impairment	Routine risk minimisation measures: • SmPC section 4.2. • PL section 2. • Recommendation to avoid the use of mexiletine in patients with creatinine clearance <30 ml/min stated in SmPC section 4.2. Additional risk minimisation measures: None	None Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Mexiletine hydrochloride 50 mg/100 mg/200 mg Hard Capsules (mexiletine hydrochloride)

This is a summary of the risk management plan (RMP) for Mexiletine hydrochloride Hard Capsules. The RMP details important risks of Mexiletine hydrochloride Hard Capsules, how these risks can be minimised, and how more information will be obtained about Mexiletine hydrochloride Hard Capsules' risks and uncertainties (missing information).

Mexiletine hydrochloride Hard Capsules' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Mexiletine hydrochloride Hard Capsules should be used.

I. THE MEDICINE AND WHAT IT IS USED FOR

Mexiletine hydrochloride Hard Capsules are authorised for the treatment of ventricular arrhythmias which are considered as life-threatening by the physician (see SmPC for the full indication). It contains mexiletine hydrochloride as the active substance and it is given by mouth.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Mexiletine hydrochloride Hard Capsules, together with measures to minimise such risks and the proposed studies for learning more about Mexiletine hydrochloride Hard Capsules' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Mexiletine hydrochloride Hard Capsules, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Mexiletine hydrochloride Hard Capsules is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Mexiletine hydrochloride Hard Capsules are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Mexiletine hydrochloride Hard Capsules. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Summary of safety concerns	
Important identified risks	• Severe cutaneous adverse reactions (SCARs) • Cardiac arrhythmia • Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine • Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment
Important potential risks	• Increased frequency of seizure episodes in patients with epilepsy • Off-label use in children
Missing information	• Effect on fertility and use in pregnancy • Safety in elderly • Use in patients with severe renal impairment

II.B Summary of important risks

Severe cutaneous adverse reactions (SCARs)	
Evidence for linking the risk to the medicine	Mexiletine is contraindicated in patients with known hypersensitivity to mexiletine, or to any of the excipients or to any local anaesthetic as there is possibility of occurrence of potentially severe cutaneous eruptions, fever, lymphadenopathy, hepatitis, haematological abnormalities with eosinophilia and atypical lymphocytes, and can involve other organs.
Risk factors and risk groups	Patients with known hypersensitivity to mexiletine or of the excipients or to any local anaesthetic are at high risk of developing SCARs.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.3, 4.4 and 4.8. • PL section 2 and 4. • How to detect early signs and symptoms of severe cutaneous adverse reactions presented in PL section 4.

Cardiac arrhythmia	
Evidence for linking the risk to the medicine	Mexiletine is a class I b antiarrhythmic drug according to the Vaughan Williams classification, and as such, it may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed. When mexiletine therapy is commenced, patients should be monitored closely (ECG, blood pressure and routine laboratory tests) over a period of at least 24 hours, and dosage adjustment made on the basis of this. Monitoring is particularly recommended in the following situations: sinus node dysfunction, conduction defects, bradycardia, hypotension or cardiac, renal or hepatic failure. Regular monitoring of cardiac function throughout treatment is advisable.
Risk factors and risk groups	If the drug is used in the following situations, the patient should be carefully monitored and the dosage may need to be reduced: sinus node dysfunction, conduction defect, bradycardia, hypotension or cardiac failure. 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.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.1, 4.3, 4.4 and 4.8. • PL section 2 and 4. • Evaluation before treatment start in order to determine if the documented ventricular arrhythmias are considered as life-threatening by the physician, stated in SmPC section 4.1. • Recommendation for initiation of treatment and monitoring by a specialist experienced in the treatment of cardiac arrhythmias, is stated in SmPC section 4.2. • Recommendation for healthcare professionals to determine the optimal dosage individually based on patient's response and tolerance is stated in SmPC section 4.2. • Recommendation for cautious use of Mexiletine in patients with hypotension or congestive heart failure because of its potential for depressing myocardial contractility is stated in SmPC section 4.4. • Recommendation for continuously monitoring in patients with second- or third-degree AV block if a ventricular pacemaker is operative, is stated in SmPC section 4.4. • Recommendation for caution when mexiletine is used in patients with first degree AV block or intraventricular conduction abnormalities is stated in SmPC section 4.4. • How patients can detect signs and symptoms of cardiac arrhythmia and when to contact an emergency centre immediately presented in PL section 4. <u>Additional risk minimisation measures</u>: • Healthcare Professional and Patient/Carer Guide

	• Patient alert card

Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine	
Evidence for linking the risk to the medicine	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) may be associated with elevations in plasma concentrations of the concomitant medicine. This 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.
Risk factors and risk groups	During the treatment with mexiletine, patients might require treatment with other concomitant medications and they can inform their healthcare professionals about ongoing treatment with mexiletine before starting any other medication. Increased concentrations of caffeine occurring with the co-administration of mexiletine may be of concern in patients with cardiac arrhythmia.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.5. • PL section 2. • Recommendation for monitoring the CYP1A2 substrate blood levels presented in section 4.5 of SmPC. • Recommendation to patients to reduce their caffeine intake by half while on treatment with mexiletine. Stated in section 2 of the PIL.

Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment	
Evidence for linking the risk to the medicine	Mexiletine is mainly (90%) metabolized in the liver, the primary pathway being CYP2D6 metabolism, although it is also a substrate for CYP1A2. Plasma elimination half-life may be prolonged in moderate to severe hepatic disease. In severe hepatic impairment, total clearance is diminished which can lead to considerable increase in plasma levels of Mexiletine and associated risk of side effects of mexiletine.
Risk factors and risk groups	Plasma elimination half-life may be prolonged in moderate to severe hepatic disease. Individual dose titration is advised in this condition. The experience with mexiletine in patients with severe hepatic impairment is limited. Therefore, mexiletine should not be used in this patient population.
Risk minimisation measures	<u>Routine risk minimisation measures</u>: • SmPC section 4.2 and 4.4. • PL section 2 and 3. • Recommendation for initiation of treatment and monitoring by a specialist experienced in the treatment of cardiac arrhythmias, stated in SmPC section 4.2. • Recommendation for healthcare professionals to determine the optimal dosage individually based on patient's response and tolerance is stated in SmPC section 4.2. • Recommendation for careful evaluation in patients in whom an abnormal liver test has occurred, or who have signs or symptoms suggesting liver dysfunction. If persistent or worsening elevation of hepatic enzymes is detected, considerations should be given to discontinuing therapy. Stated in section 4.4 of SmPC. <u>Additional risk minimisation measures</u>: • Healthcare Professional and Patient/Carer Guide

Increased frequency of seizure episodes in patients with epilepsy	
Evidence for linking the risk to the medicine	Common elements of pathogenesis create a basis for the assumption that antiarrhythmic drugs (AADs) may affect seizure phenomena and interact with antiepileptic drugs (AEDs).
Risk factors and risk groups	Patients with known history of epilepsy and on antiepileptic drugs (AEDs).
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 and 4.8. • PL section 2. • Recommendation for use with caution in patients with history of seizures. Stated in section 4.4 of SmPC.

Off-label use in children	
Evidence for linking the risk to the medicine	Ventricular arrhythmias may occur at all ages, including childhood and adolescence. Therefore, the possibility of off-label use in the paediatric population cannot be excluded.
Risk factors and risk groups	Children with ventricular arrhythmias which are considered as life-threatening by the physician may be at risk of off-label use as paediatric clinicians may want to use mexiletine in the paediatric population (children and adolescent aged 0 to 18 years).
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.2 and 5.1. • PL section 2 and 3.

Effect on fertility and use in pregnancy	
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.6. • PIL section 2. •

Safety in elderly	
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.2. • PIL section 3. • Recommendation for healthcare professionals: Treatment with mexiletine should be initiated and monitored by a specialist experienced in the treatment of cardiac arrhythmias. The optimal dosage should be determined individually based on the patient's response and tolerance. Stated in section 4.2 of SmPC.

Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.2. • PIL section 2. • Recommendation to avoid the use of mexiletine in patients with creatinine clearance <30 ml/min, stated in SmPC section 4.2. •

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules.

PART VII: ANNEXES

ANNEX 1 – EUDRAVIGILANCE INTERFACE

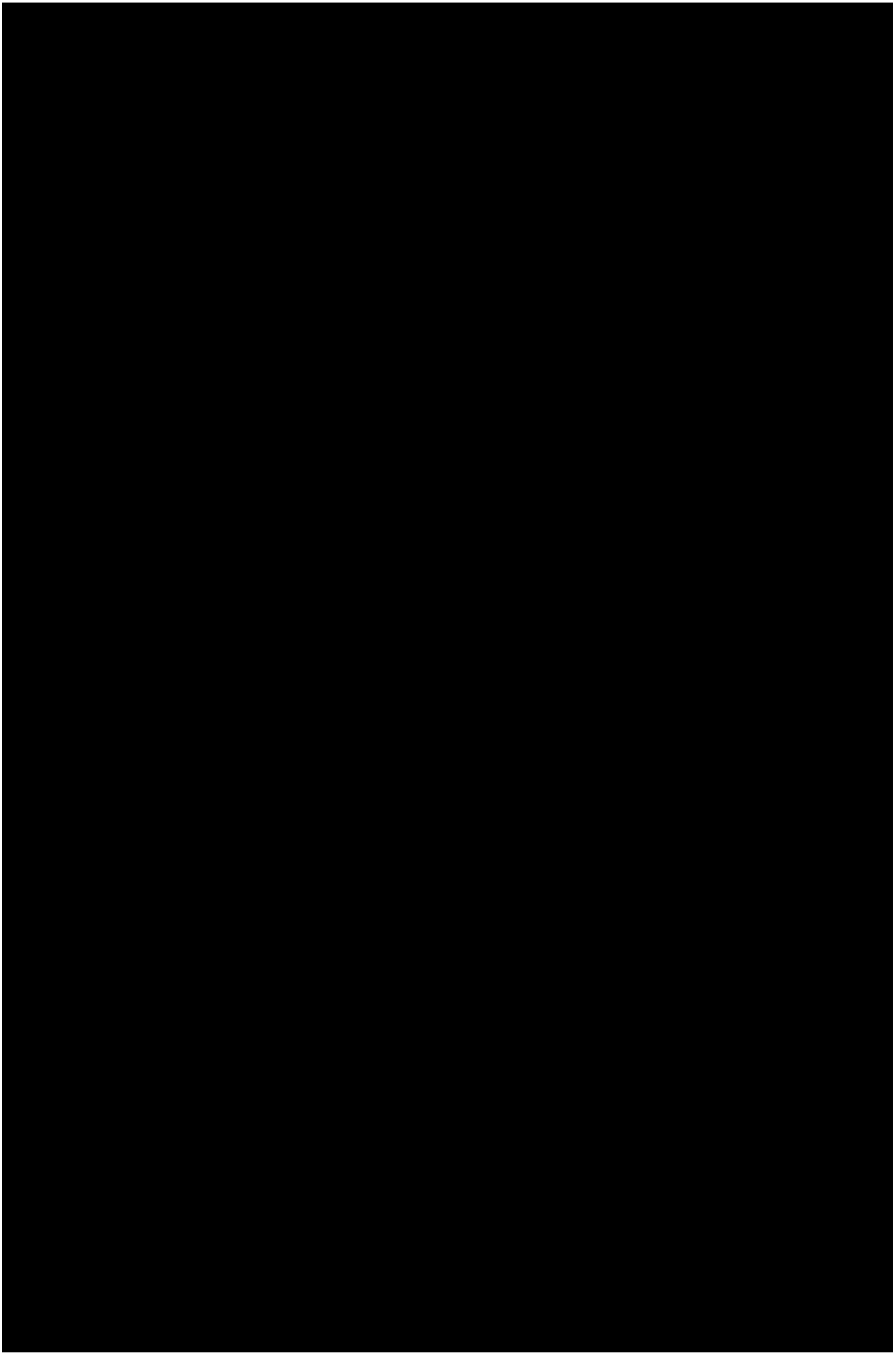
This Annex is not applicable.

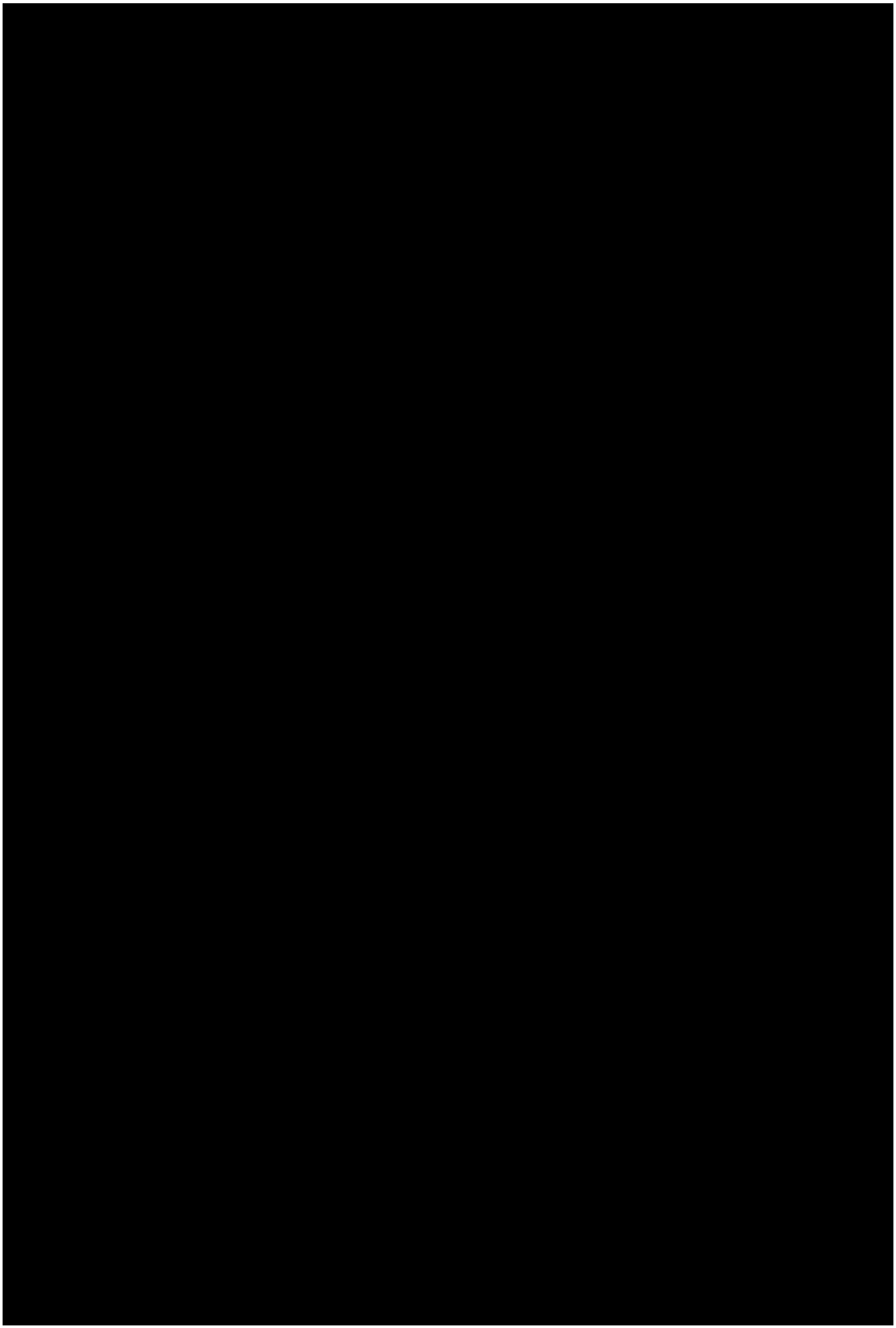
ANNEX 2 – TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

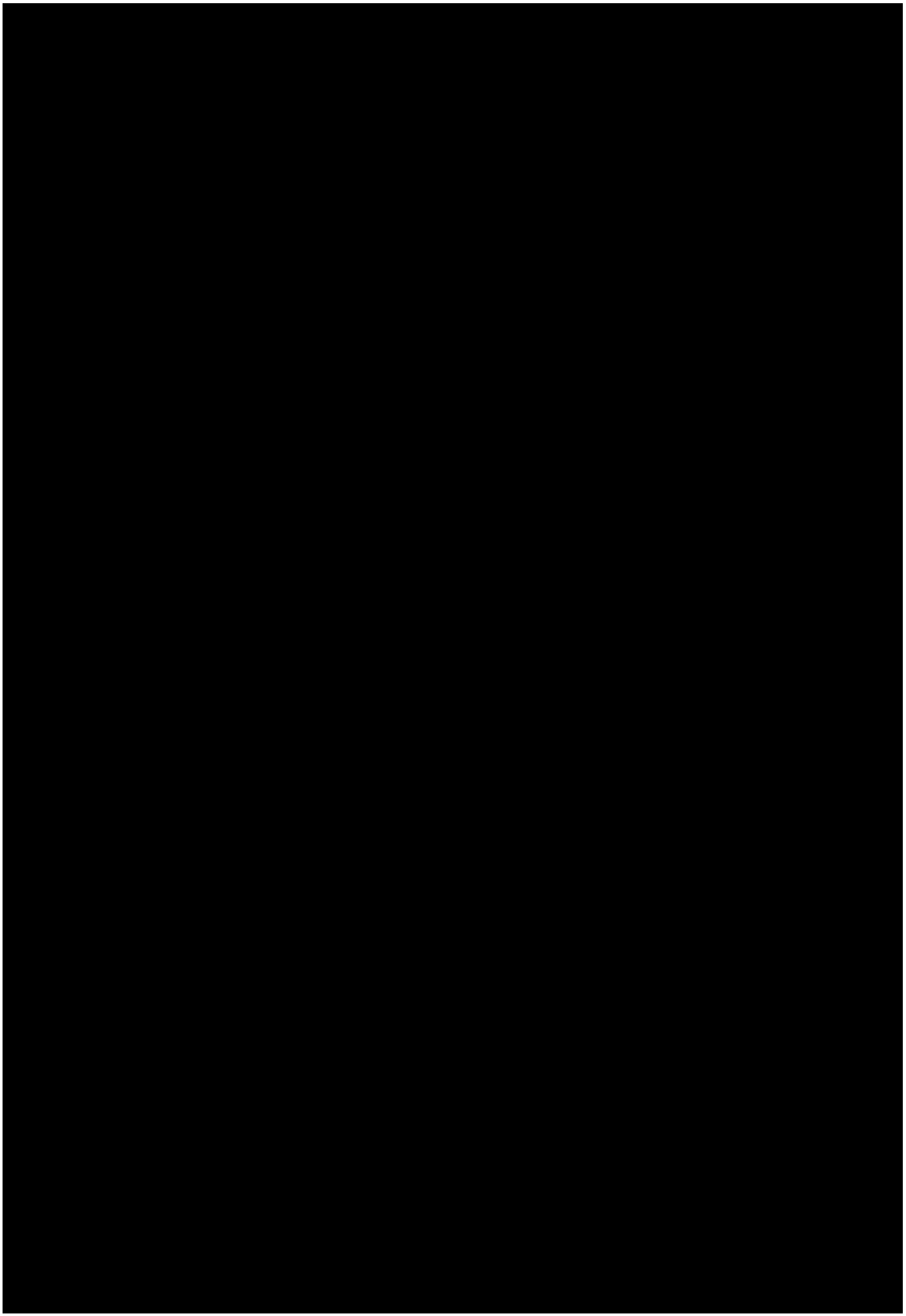
This Annex is not applicable.

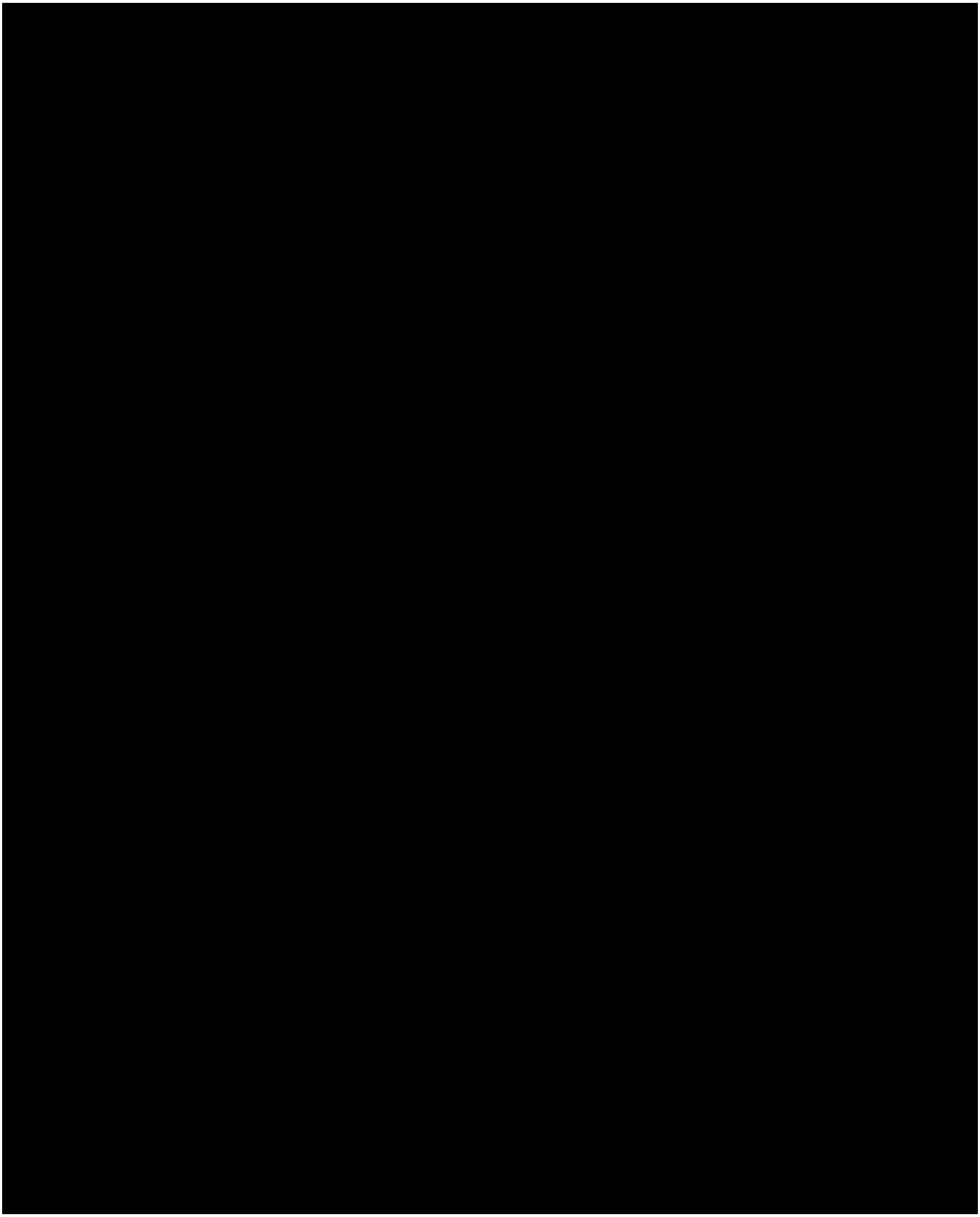
ANNEX 3 - PROTOCOLS FOR PROPOSED, ON-GOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

This Annex is not applicable.









ANNEX 5 - PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

This Annex is not applicable.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Draft key messages of the additional risk minimisation measures

Physician educational material:

- **The Summary of Product Characteristics**
- **Guide for healthcare professionals**

In order to prevent and / or minimise the important identified risks of Cardiac Arrhythmia in patients with ventricular arrhythmias (which are considered as life-threatening by the physician) and decreased Mexiletine hydrochloride clearance, thus the risk of adverse reactions in patients with hepatic impairment, the MAH shall ensure that all healthcare professionals (HCPs) and patients are provided, respectively, with:

• Educational guide for HCPs;

• Patient alert card

The Educational guide for HCPs, which should always be read in conjunction with the Summary of Product Characteristics (SmPC) before prescribing Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules, should contain the following key elements:

• Information about the risk of cardiac arrhythmias in patients using Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules;

• Guidance to identify (and exclude) patients at a greater risk of developing arrhythmias due to Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules treatment;

• Contraindications with Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules which may increase the susceptibility to arrhythmias;

• Before starting treatment, HCPs should perform a detailed and careful cardiac evaluation in all patients, in order to determine the cardiac tolerability of Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules. Furthermore, electrolytic evaluation should be done prior to initiating therapy with mexiletine in every patient and electrolyte imbalance needs to be corrected before administering mexiletine.

A cardiac evaluation is also recommended shortly after starting Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules (e.g. within 48 hours).

• Throughout treatment with Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules:

- A detailed cardiac evaluation (including ECG) should be carried out before and after any dose increase. During Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules maintenance treatment, a detailed cardiac evaluation, including ECG should be carried out every 24-48 hour. Holter-monitoring and echocardiography are recommended at least annually, or more frequently, if considered necessary, as part of routine cardiac assessment.
- Electrolyte imbalance needs to be monitored throughout treatment (with a periodicity to be adapted patient by patient).

• Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules should be stopped immediately if the patient develops cardiac abnormalities, is not responding or experiencing benefit within Mexiletine hydrochloride long-term treatment;

• Highlight the risk of decreased Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules clearance in patients with hepatic impairment and provide guidance on how to treat those patients

in order to prevent it, ensuring Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules cautious titration in patients with moderate or severe hepatic impairment. Patients in whom pathologically high liver values have been established or who have signs or symptoms of impaired liver function, should be monitored carefully.

• HCPs should counsel patients on:

- The risk of cardiac arrhythmias (informing about symptoms of arrhythmias, advising patients to contact immediately their HCP, or emergency centres, if they experience any of these symptoms);
- The risk of decreased Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules clearance in patients with hepatic impairment (advising patients to inform their HCP if they have any underlying hepatic disorder);

• Reporting of adverse reactions in patients using Mexiletine hydrochloride 50 mg, 100 mg, 200 mg Hard Capsules.

- **Patient alert card**

  The patient alert card (wallet size), to be handed by prescribing specialist and to be read in conjunction with the patient leaflet, should contain the following key messages:

  - Patients should carry the card at all times, and show it at all medical visits to HCPs other than the prescriber (e.g. emergency HCPs);

  - Prompts to enter the contact details of the patient, the treating physician, and Mexiletine treatment starting date;

  - Inform patients that, before starting and throughout treatment with Mexiletine, HCPs should perform a detailed and careful cardiac evaluation;

  - Patients should inform the HCP about any ongoing medications or before starting any new medication, while on treatment with Mexiletine;

  - Information about symptoms of cardiac arrhythmias, which can be life-threatening, and when patients should seek HCP attention;

  - Patients should not exceed the dose prescribed by their doctor and should not take a double dose to make up for a forgotten dose;

ANNEX 7 - OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

[redacted]

ANNEX 8 – SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

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