UK Risk Management Plan for Mexiletine hydrochloride 100 mg and 200 mg hard capsules

RMP version to be assessed as part of this application:

RMP Version number: 0.2

Data lock point for this RMP: [redacted]

Date of final sign-off: [redacted]

Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation applications (MAAs).

Summary of significant changes in this RMP: Not applicable.

QPPV name: [redacted]

QPPV signature: [redacted]

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Mexiletine hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	Cardiac therapy, antiarrhythmics, Class Ib ATC code: C01BB02
Marketing Authorisation Applicant	Waymade Plc
Medicinal products to which this RMP refers	2
Invented name(s) in the United Kingdom (UK)	Mexiletine hydrochloride 100 mg hard capsules Mexiletine hydrochloride 200 mg hard capsules
Marketing authorisation procedure	National procedure
Brief description of the product	*Chemical class:* Class Ib antiarrhythmic agent.
	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: Not applicable.
Hyperlink to the Product Information	The product information including the SmPC and the PIL is included in Module 1.3.1 of the eCTD.
Indication(s) in the UK	Current: Mexiletine is indicated for the treatment of documented ventricular arrhythmias which, in the judgement of the physician, are considered as life-threatening.
	Proposed: Not applicable.

Dosage in the UK	Current: *Adults:* The optimal dosage should be determined individually based on the patient's response and tolerance. 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.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	100 mg and 200 mg hard capsules
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the UK?	No.

Part II: Safety specification

Modules SI to SVI are not applicable for initial marketing authorisation applications (MAA) involving well-established use medicinal products.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable.

Part II: Module SIII - Clinical trial exposure

Not applicable.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable.

Part II: Module SV - Post-authorisation experience

Not applicable.

Part II: Module SVI - Additional UK requirements for the safety specification

Not applicable.

Part II: Module SVII - Identified and potential risks

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

Currently there are a number of approved products with the active substance mexiletine hydrochloride on the market. Namuscla® and Dopital® are currently registered in the European Union (EU). Mexiletine hydrochloride hard capsules are also registered in the UK, mexiletine hydrochloride 50 mg, 100 mg and 200 mg hard capsules (Clinigen healthcare Ltd).

Mexiletine hydrochloride is a medicinally well-established product with recognised efficacy and an acceptable level of safety when used within the recommendations. The overall safety of mexiletine hydrochloride 100 mg and 200 mg hard capsules as recommended is well-established and detailed in the published literature.

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
- 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 the UK where the product is authorised):

- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine
- Effect on mexiletine levels due to CYP2D6 polymorphism and smoking
- Livery injury
- Use in patients with severe renal impairment
- Use in patients with electrolyte disturbances
- Use in patients with congestive heart failure, conduction abnormalities or hypotension.

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

Important Identified Risk 1: Cardiac arrhythmia

Risk-benefit impact:

Mexiletine hydrochloride has the potential for depressing myocardial contractility. This may lead to cardiac arrhythmias in patients with existing cardiac disorders. Therefore, treatment with mexiletine hydrochloride should be initiated and monitored appropriately. Because of the above, caution should also be exercised when mexiletine hydrochloride is used in patients with first degree atrioventricular block (AV block) or intraventricular conduction abnormalities. If a ventricular pacemaker is operative, patients with second- or third-degree AV block may be treated with mexiletine hydrochloride, if continuously monitored.
Co-administration of mexiletine hydrochloride and antiarrhythmics inducing torsades de pointes and other classes of antiarrhythmics (Class Ib: lidocaine, phenytoin, tocainide; Class II: propranolol, esmolol, timolol, metoprolol, atenolol, crvedilol, bisoprolol, nebivolol; Class IV: verapamil, diltiazem) increases the risk of adverse cardiac reactions. Therefore, appropriate management is advised when prescribing mexiletine hydrochloride in patients taking other antiarrhythmics.

Important Identified Risk 2: Risk of decreased mexiletine clearance in patients with hepatic impairment

Risk-benefit impact:

Abnormalities of the liver function and rare instances of severe liver injury, including hepatic necrosis have been reported in association with mexiletine hydrochloride treatment. It is recommended that patients in whom an abnormal liver test has occurred, or who have signs or symptoms suggesting liver dysfunction should be carefully evaluated. If persistent or worsening elevation of hepatic enzymes is detected, considerations should be given to discontinuing therapy.

It is recommended to exercise caution in patients with mild or moderate hepatic impairment due to the potential for higher plasma exposure. In these patients, a minimum of two weeks between dose

adjustments is recommended. Mexiletine hydrochloride should not be used in patients with severe hepatic impairment.

Important Identified Risk 3: Blood dyscrasias

Risk-benefit impact:

Leukopenia and thrombocytopenia have been reported in clinical studies. It is recommended that careful hematologic monitoring should be carried out prior to initiating therapy in patients on mexiletine hydrochloride. If significant hematologic changes are observed, the patient should be carefully evaluated, and, if warranted, mexiletine hydrochloride should be discontinued. Blood counts usually returned to normal within one month of discontinuation.

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

Risk-benefit impact:

Mexiletine hydrochloride can increase the frequency of seizure episodes. Mexiletine hydrochloride hard capsules should be used with caution in patients with history of seizures.

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

Not applicable.

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

Important identified risk	**Cardiac arrhythmia**
Potential mechanisms	Mexiletine hydrochloride 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. These adverse effects are directly linked to blockade of sodium channels. A continuously rising number of cardiac and non-cardiac agents have been implicated in proarrhythmia and SCD (sudden cardiac death). Abnormalities in repolarisation and/or depolarisation of cardiac cells through changes in ion channels and myocardial zones are the main pathophysiological mechanisms manifested as long QT, short QT and Brugada syndrome (BS) in routine clinical practice. Mexiletine hydrochloride is included in the drugs implicated in QT interval prolongation and torsades de pointes [redacted]
Evidence source(s) and strength of evidence	Literature and product information of products with the same active substance.
Characterisation of the risk	Typical symptoms of cardiac arrhythmia include: palpitations, chest pain, shortness of breath, light-headedness, dizziness, and fainting. In severe cases cardiac arrhythmia, may even result in collapse and sudden cardiac arrest.

Important identified risk	**Cardiac arrhythmia**
	One of the serious reported adverse reactions in patients treated with mexiletine hydrochloride 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. 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 hydrochloride.
Risk factors and risk groups	Patients with preexisting cardiac conduction anomalies. The concomitant use of mexiletine and antiarrhythmic drugs. Coadministration of hepatic enzymes (CYP1A2 and CYP2D6) inhibitors (such as ciprofloxacin, fluvoxamine, propafenone or quinidine).
Preventability	The risk can be minimised by providing supportive information to the prescriber (SmPC, healthcare professional guide, and patient alert card)_and the patient (patient information leaflet, and patient alert card).
Impact on the risk-benefit balance of the product	The safety profile of mexiletine hydrochloride in the antiarrhythmic indications is well-established. There may be a remaining risk that mexiletine hydrochloride triggers arrhythmia or aggravate an existing arrhythmia, especially if not prevented and managed appropriately. 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) (Waymade mexiletine hydrochloride SmPC).
Public health impact	No important impact expected.

Important identified risk	**Risk of decreased mexiletine clearance in patients with hepatic impairment**
Potential mechanisms	Mexiletine hydrochloride is mainly (90%) metabolised 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

Important identified risk	**Risk of decreased mexiletine clearance in patients with hepatic impairment**
	can lead to considerable increase in plasma levels of mexiletine hydrochloride and associated risk of an increase in side effects of mexiletine hydrochloride [redacted]
Evidence source(s) and strength of evidence	Literature and product information of products with the same active substance.
Characterisation of the risk	The increased level of mexiletine hydrochloride can lead to an increase of all adverse events of mexiletine hydrochloride.
Risk factors and risk groups	Patients with all grades of hepatic disorders that lead to hepatic dysfunction.
Preventability	The risk is minimised by providing supportive information to the prescriber (SmPC, and healthcare professional guide) and the patient (patient information leaflet). Individual dose titration is advised in moderate to severe hepatic disease. Mexiletine hydrochloride 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 hydrochloride 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. The expected incidence rate of drug-induced liver injury, liver disorder, hepatitis is < 1/10,000 patients (classified as a very rare adverse reaction) (Waymade mexiletine hydrochloride SmPC).
Public health impact	No important impact on public health expected.

Important identified risk	**Blood dyscrasias**
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	Leukopenia and thrombocytopenia have been reported in clinical studies (SmPC). Among 10,867 patients treated with mexiletine hydrochloride in the compassionate use program, marked leukopenia (neutrophils less than 1000/mm^3) or agranulocytosis were seen in 0.06% and milder depressions of leukocytes were seen in 0.08%, and thrombocytopenia was observed in 0.16%. Marked leukopenia or agranulocytosis did not occur in any patient receiving mexiletine hydrochloride alone, but were associated

Important identified risk	**Blood dyscrasias**
	with patient's underlying disease and concomitant medications [redacted] The expected incidence rate of neutropenia, agranulocytosis is > 1/10,000 to < 1/1,000 patients (classified as a rare adverse reaction). The expected incidence rate of leukopenia and thrombocytopenia is not known (Waymade mexiletine hydrochloride SmPC).
Characterisation of the risk	Blood dyscrasias include a variety of conditions that affect blood components, bone marrow, lymph tissue, or blood vessels. These conditions can be cancerous or benign, and they can range from mild to life-threatening. Blood dyscrasias may be caused by various factors such as medications, infections, or genetic conditions [redacted]
Risk factors and risk groups	All patients receiving mexiletine hydrochloride.
Preventability	The risk is minimised by providing supportive information to the prescriber (SmPC, and healthcare professional guide) and the patient (patient information leaflet). Haemogram including white blood cells (WBC) differential and platelet count should be performed prior to initiation of therapy. Careful hematologic monitoring should be carried out. If significant haematologic changes are observed, the patient should be carefully evaluated, and, if warranted, mexiletine hydrochloride should be discontinued.
Impact on the risk-benefit balance of the product	Blood counts usually return to normal within one month of discontinuation. With appropriately monitoring and managing the patients, and with the low incidence, no important impact on the risk-benefit balance is expected.
Public health impact	No impact expected on public health.

Important potential risk	**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

Important potential risk	**Increased frequency of seizure episodes in patients with epilepsy**
	reports illustrate arrhythmogenic effect of some AEDs [redacted]
Evidence source(s) and strength of evidence	Literature and product information of products with the same active substance.
Characterisation of the risk	Mexiletine hydrochloride can increase the frequency of seizure episodes. The expected incidence rate of seizure episodes is between ≥ 1/1,000 to < 1/100 patients (classified as an uncommon adverse reaction) (Waymade mexiletine hydrochloride SmPC).
Risk factors and risk groups	Patients with known history of epilepsy and on AEDs.
Preventability	Mexiletine hydrochloride capsules should be used with caution in patients with history of seizures.
Impact on the risk-benefit balance of the product	There is some impact on the benefit-risk for patients with pre-existing seizure disorders as mexiletine hydrochloride can worsen seizures in these patients.
Public health impact	No important impact on public health expected.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Cardiac arrhythmia • Risk of decreased mexiletine clearance in patients with hepatic impairment • Blood dyscrasias
Important potential risks	• Increased frequency of seizure episodes in patients with epilepsy
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the medicinal product.

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. This 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 follow-up form is presented in Annex 4 of the RMP.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are proposed that are imposed as condition of the marketing authorisation (category 1), as specific obligations in the context of a marketing authorisation under exceptional circumstances or conditional marketing authorisation (category 2) or required by the competent authority (category 3).

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

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**
Cardiac arrhythmia	Routine risk communication: *SmPC sections 4.1, 4.2, 4.3, 4.4, and 4.8.* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk:*Recommendation for healthcare professionals to determine the optimal dosage individually based on patient's response and tolerance in SmPC section 4.2* *Recommendation for continuously monitoring in patients with second- or third-degree AV block if a ventricular pacemaker is operative 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 decreased mexiletine clearance in patients with hepatic impairment	Routine risk communication: *SmPC sections 4.24.4, 4.5 , 4.8, and 5.2* *PL sections 2, 3, and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for healthcare professionals to determine the optimal dosage individually based on patient's response and tolerance 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 in section 4.4 of SmPC* Other routine risk minimisation measures beyond the Product Information: Legal status: *Prescription only medicine*
Blood dyscrasias	*SmPC sections 4.4, and 4.8* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for careful hematologic monitoring in patients on mexiletine hydrochloride 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	*SmPC sections 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 in section 4.4 of SmPC*

	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 guide

Objectives:

This educational guide is provided to healthcare professionals (HCPs) to help ensure safe and effective use of mexiletine hydrochloride and to highlight the risk of cardiac arrhythmia and the risk of adverse reactions in patients with reduced mexiletine hydrochloride clearance due to hepatic dysfunction.

Rationale for the additional risk minimisation activity:

The guide aims to educate HCPs and to communicate the importance of monitoring cardiac events in all patients before initiation and during treatment with mexiletine hydrochloride. It is important to determine optimal dosage based on the patient's response and tolerance. The HCPs are advised to be cautious with dosing of patients with hepatic dysfunction to minimise the risk of adverse reactions due to reduced mexiletine hydrochloride clearance in these patients. Mexiletine hydrochloride should not be used in patients with severe hepatic impairment.

Target audience and planned distribution path:

Healthcare professionals prescribing and monitoring mexiletine hydrochloride in patients (e.g. Cardiologists, Anaesthesiologists, Intensive Care Unit Physicians).
Distribution path: The healthcare professional guide will be made available on the electronic medicines compendium website (https://www.medicines.org.uk/emc). Healthcare professionals can download at the time of initiation of treatment.

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:

This patient alert card provides patients with additional information on the risk of cardiac arrhythmia (irregular heartbeat) with mexiletine hydrochloride. 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 100 mg, 200 mg hard capsules contain mexiletine hydrochloride and some patients taking mexiletine hydrochloride may develop cardiac arrhythmia which can be life-threatening. The 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 hydrochloride 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	Risk minimisation measures	Pharmacovigilance activities
Cardiac arrhythmia	Routine risk minimisation measures: *SmPC sections 4.3, 4.4, and 4.8.* *PL sections 2 and 4* *SmPC section 4.2 where recommendation is given to determine the optimal dosage individually* *SmPC section 4.4 where recommendation is given for continuously monitoring in patients with second- or third-degree AV block if a ventricular pacemaker is operative* *PL section 4 where it is described how how patients can detect signs and symptoms of cardiac arrhythmia and when to contact an emergency centre immediately* Legal status Additional risk minimisation measures: *Healthcare professional 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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Risk of decreased mexiletine clearance in patients with hepatic impairment	*SmPC sections 4.24.4, 4.5 , 4.8, and 5.2* *PL sections 2, 3, and 4* *SmPC section 4.2. where recommendation is given for healthcare professionals to determine the optimal dosage individually* *SmPC section 4.4 where recommendation is given for careful evaluation in patients in whom an abnormal liver test has occurred, or who have signs or symptoms suggesting liver dysfunction.* Legal status Additional risk minimisation measures: *Healthcare professional guide*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Blood dyscrasias	*SmPC sections 4.4, and 4.8* *PL sections 2 and 4* *SmPC section 4.4 where recommendation is given for careful hematologic monitoring* Legal status Additional risk minimisation measures: *Healthcare professional guide*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Increased frequency of seizure episodes in patients with epilepsy	*SmPC sections 4.4, and 4.8* *PL section 2* Legal status Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Mexiletine hydrochloride 100 mg and 200 mg hard capsules (mexiletine hydrochloride)

This is a summary of the risk management plan (RMP) for Mexiletine hydrochloride 100 mg and 200 mg hard capsules (mexiletine hydrochloride). The RMP details important risks of Mexiletine hydrochloride, how these risks can be minimised, and how more information will be obtained about Mexiletine hydrochloride's risks and uncertainties (missing information).

Mexiletine hydrochloride's 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.

Important new concerns or changes to the current ones will be included in updates of Mexiletine hydrochloride 's RMP.

I. The medicine and what it is used for

Mexiletine hydrochloride is authorised for the treatment of documented ventricular arrhythmias which, in the judgement of the physician, are considered as life-threatening. It contains mexiletine hydrochloride as the active substance, and it is given orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Mexiletine hydrochloride, together with measures to minimise such risks and the proposed studies for learning more about Mexiletine hydrochloride's 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, 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*.

II.A List of important risks and missing information

Important risks of Mexiletine hydrochloride 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. 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):

List of important risks and missing information	
Important identified risks	• Cardiac arrhythmia • Risk of decreased mexiletine clearance in patients with hepatic impairment • Blood dyscrasias
Important potential risks	• Increased frequency of seizure episodes in patients with epilepsy
Missing information	• None

II.B Summary of important risks

Cardiac arrhythmia	
Evidence for linking the risk to the medicine	Literature and product information of products with the same active substance.
Risk factors and risk groups	Patients with preexisting cardiac conduction anomalies. The concomitant use of mexiletine and antiarrhythmic drugs. Coadministration of hepatic enzymes (CYP1A2 and CYP2D6) inhibitors (such as ciprofloxacin, fluvoxamine, propafenone or quinidine).
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3, 4.4, and 4.8.* *PL sections 2 and 4* *SmPC section 4.2 where recommendation is given to determine the optimal dosage individually* *SmPC section 4.4 where recommendation is given for continuously monitoring in patients with second- or third-degree AV block if a ventricular pacemaker is operative* *PL section 4 where it is described how patients can detect signs and symptoms of cardiac arrhythmia and when to contact an emergency centre immediately* Legal status Additional risk minimisation measures: *Healthcare professional guide* *Patient alert card*

Risk of decreased mexiletine clearance in patients with hepatic impairment	
Evidence for linking the risk to the medicine	Literature and product information of products with the same active substance.
Risk factors and risk groups	Patients with all grades of hepatic disorders that lead to hepatic dysfunction.
Risk minimisation measures	*SmPC sections 4.2, 4.4, 4.5 , 4.8, and 5.2* *PL sections 2, 3, and 4* *SmPC section 4.2. where recommendation is given for healthcare professionals to determine the optimal dosage individually* *SmPC section 4.4 where recommendation is given for careful evaluation in patients in whom an abnormal liver test has occurred, or who have signs or symptoms suggesting liver dysfunction.* Legal status Additional risk minimisation measures: *Healthcare professional guide*

Blood dyscrasias	
Evidence for linking the risk to the medicine	Leukopenia and thrombocytopenia have been reported in clinical studies (SmPC). Among 10,867 patients treated with mexiletine hydrochloride in the compassionate use program, marked leukopenia (neutrophils less than 1000/mm^3) or agranulocytosis were seen in 0.06% and milder depressions of leukocytes were seen in 0.08%, and thrombocytopenia was observed in 0.16%. Marked leukopenia or agranulocytosis did not occur in any patient receiving mexiletine hydrochloride alone, but were associated with patient's underlying disease and concomitant medications [redacted] The expected incidence rate of neutropenia, agranulocytosis is > 1/10,000 to < 1/1,000 patients (classified as a rare adverse reaction). The expected incidence rate of leukopenia and thrombocytopenia is not known (Waymade mexiletine hydrochloride SmPC).
Risk factors and risk groups	All patients receiving mexiletine hydrochloride.
Risk minimisation measures	*SmPC sections 4.4, and 4.8* *PL sections 2 and 4* *SmPC section 4.4 where recommendation is given for careful hematologic monitoring* Legal status Additional risk minimisation measures: *Healthcare professional guide*

Increased frequency of seizure episodes in patients with epilepsy	
Evidence for linking the risk to the medicine	Literature and product information of products with the same active substance.
Risk factors and risk groups	Patients with known history of epilepsy and on AEDs.
Risk minimisation measures	*SmPC sections 4.4, and 4.8* *PL section 2* Legal status Additional risk minimisation measures: *None*

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.

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

There are no studies required for Mexiletine hydrochloride.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not applicable.

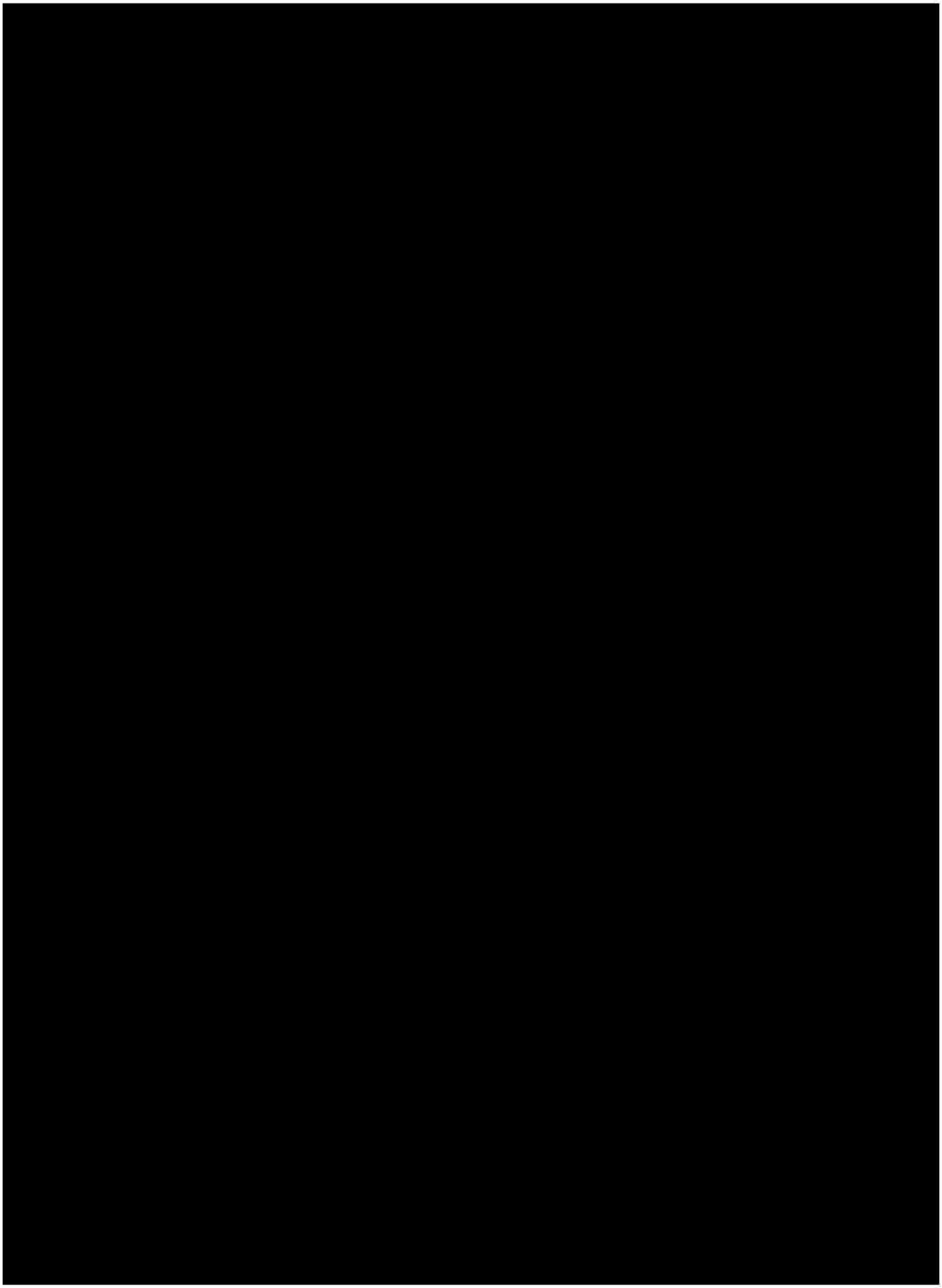
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

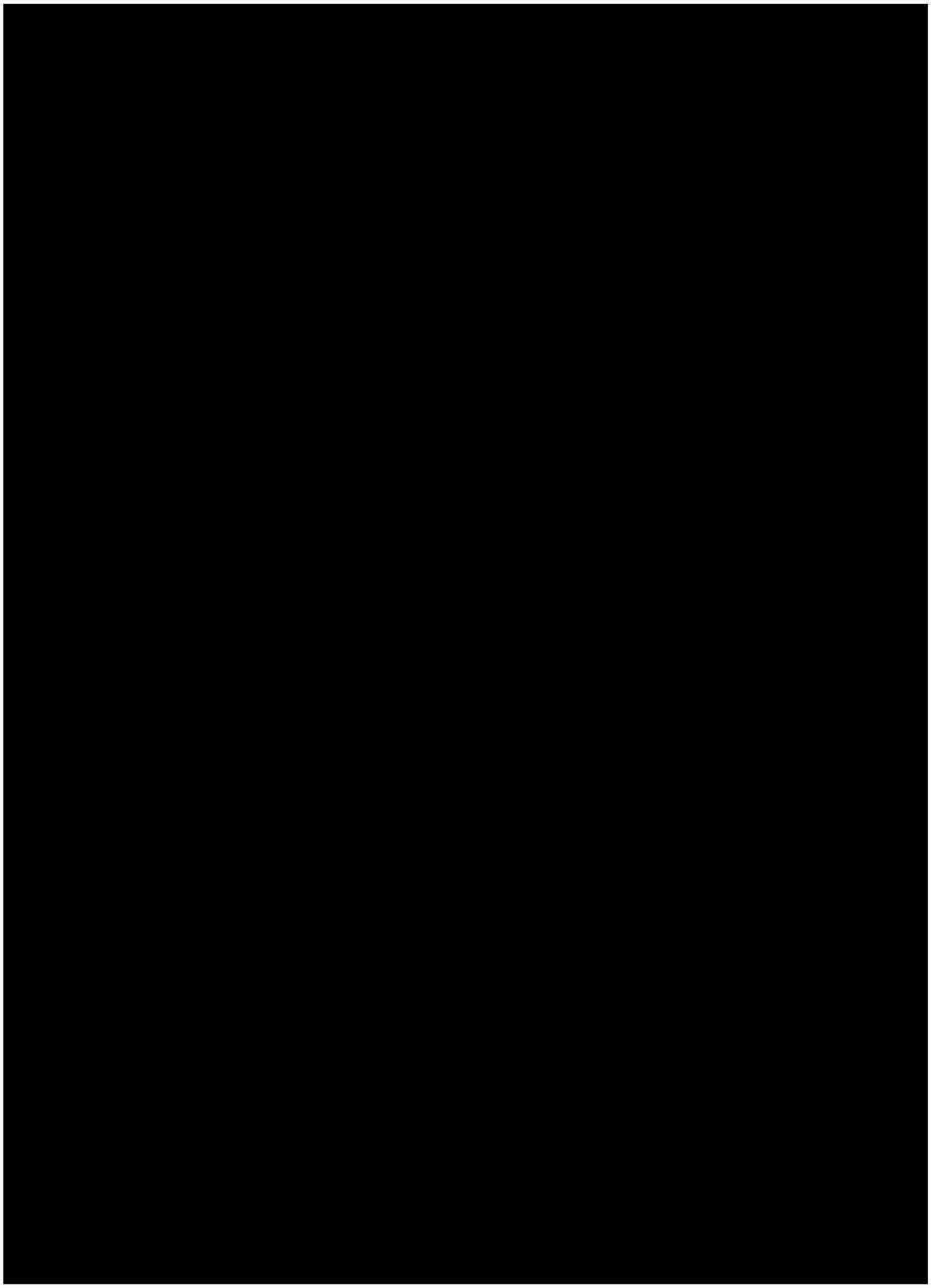
Not applicable.

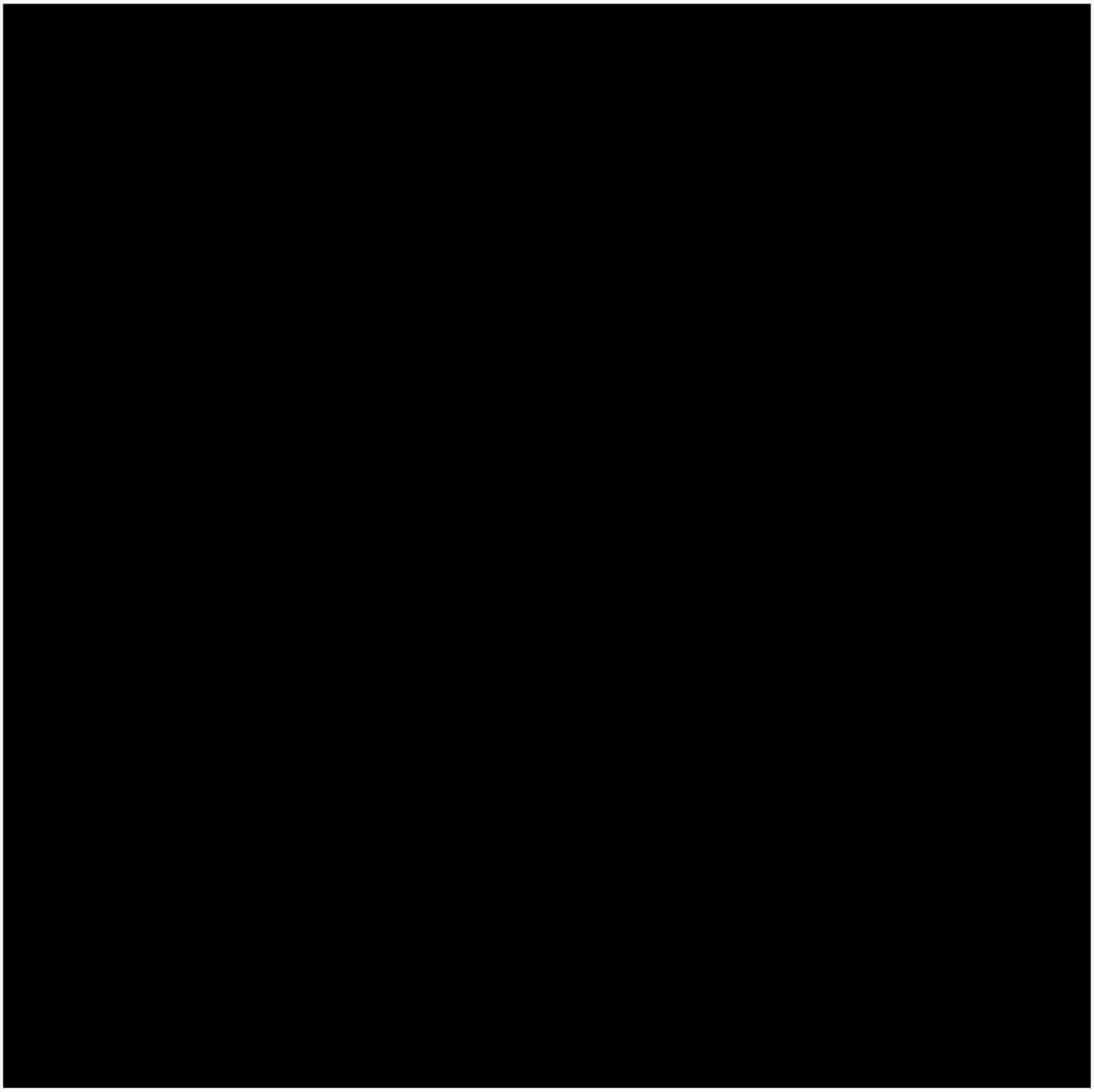
Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

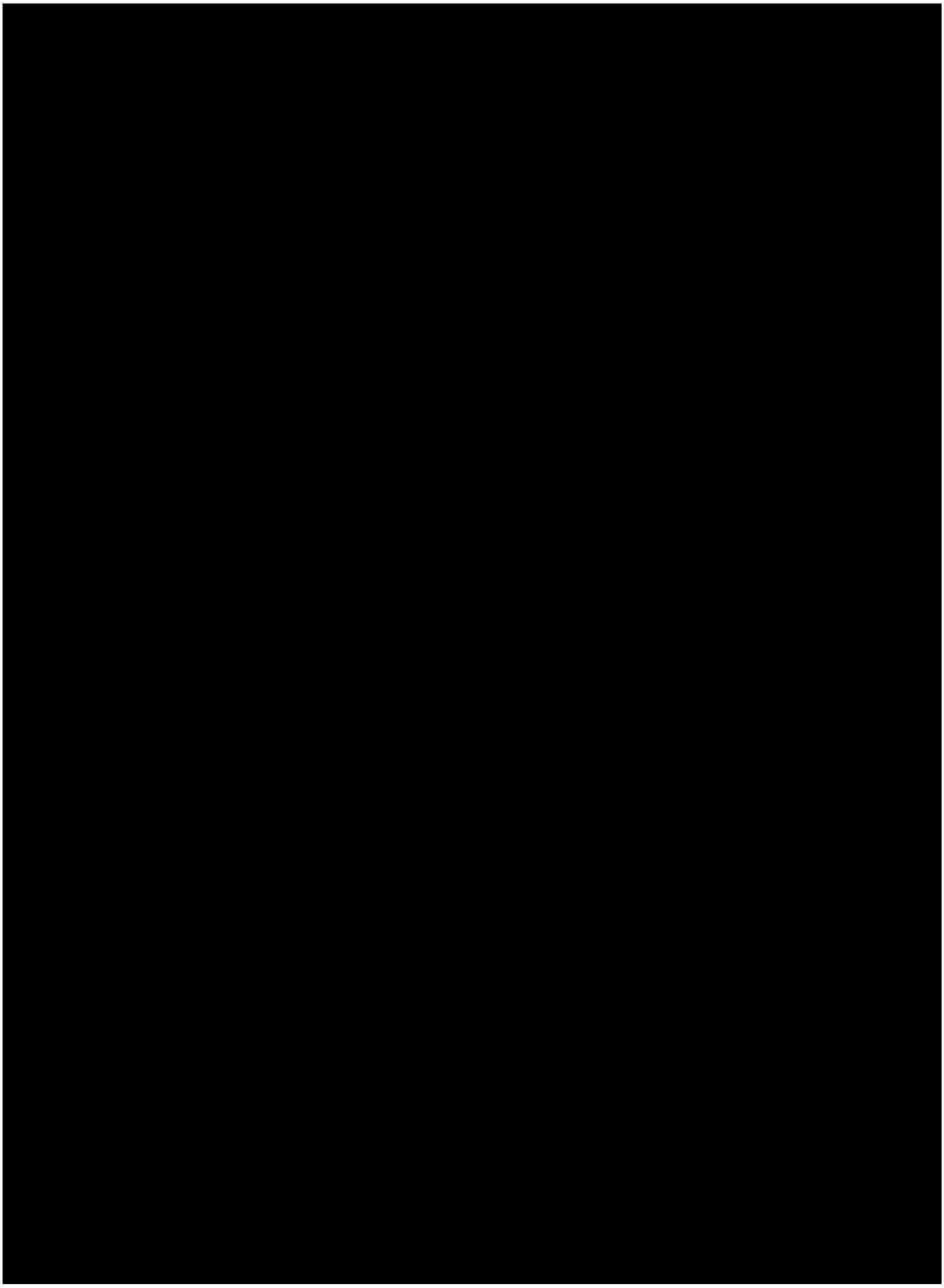






Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.



Annex 7 - Other supporting data (including referenced material)

Annex 8 – Summary of changes to the risk management plan over time

Not applicable.