Part VI: Summary of the risk management plan

Summary of risk management plan for Dronedarone Aristo [dronedarone (as hydrochloride)]

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

Dronedarone's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how dronedarone should be used.

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

I. The medicine and what it is used for

Dronedarone is authorised for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF) (see SmPC for the full indication). It contains dronedarone (as hydrochloride), as the active substance and it is given by oral route of administration of 400 mg film-coated tablets.

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

Important risks of dronedarone, together with measures to minimise such risks and the proposed studies for learning more about dronedarone'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 dronedarone, 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, including PSUR assessment 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 dronedarone is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of dronedarone are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 dronedarone. 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	• Heart failure (including use in patients with unstable hemodynamic conditions with history of, or current heart failure or left ventricular systolic dysfunction, and pre-renal azotemia) • Use in permanent atrial fibrillation (use in patients with AF duration ≥6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician) • Drug-Drug Interactions with potent CYP3A4 inhibitors • Bleeding with INR increase, in association with drug modifying INR (warfarin) • Interstitial lung disease (ILD) • Hepatotoxicity
Important potential risks	• Inappropriate anticoagulation • Nephrotoxicity • **Drug-Drug Interactions, with:** o Digitalis o Calcium antagonists with heart rate lowering properties o Beta-blockers o Statins o Tacrolimus and sirolimus o Potent CYP3A4 inducers o Dabigatran • **Amiodarone-like effects:** o Photosensitivity disorders and pigmentation disorders (extended to severe skin disorders) o Neuropathy, including Optic Neuropathy

List of important risks and missing information	
	• **Preclinical finding:** o Prolactin-induced mammary carcinogenesis
Missing information	• Effect in pregnancy • Effect in lactation • Effect in severe hepatic impairment • Effect in children (potential off-label use)

II.B Summary of important risks

Heart failure (including use in patients with unstable hemodynamic conditions, or history of, or current heart failure or left ventricular systolic dysfunction, and pre-renal azotemia) **Important identified risk**	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3 and 4.4.* – Prescription only medicine. Additional risk minimisation measures: *Education and reminder tool: Prescriber Guide*

Use in permanent atrial fibrillation (use in patients with AF duration ≥6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician) **Important identified risk**	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3 and 4.4.* – Prescription only medicine. Additional risk minimisation measures: *Education and reminder tool: Prescriber Guide*

Drug-Drug Interactions with potent CYP3A4 inhibitors **Important identified risk**	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.3, 4.4 and 4.5.* – Prescription only medicine.

	Additional risk minimisation measures: *Education and reminder tool: Prescriber Guide*

Bleeding with INR increase, in association with drug modifying INR (warfarin) **Important identified risk**	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4 and 4.5.* – Prescription only medicine. Additional risk minimisation measures: *Education and reminder tool: Prescriber Guide*

Interstitial lung disease (ILD) **Important identified risk**	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3, 4.4 and 4.8.* – Prescription only medicine. Additional risk minimisation measures: *Education and reminder tool: Prescriber Guide*

Hepatotoxicity **Important identified risk**	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3 and 4.4.* – Prescription only medicine. Additional risk minimisation measures: *Education and reminder tool: Prescriber Guide*

Inappropriate anticoagulation **Important potential risk**	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4.* – Prescription only medicine. Additional risk minimisation measures:

	Education and reminder tool: Prescriber Guide

Nephrotoxicity **Important potential risk**	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3 and 4.4.* – Prescription only medicine. Additional risk minimisation measures: *Education and reminder tool: Prescriber Guide*

Drug-Drug Interactions with digitalis, calcium antagonists with heart rate lowering properties, beta blockers, statins, tacrolimus and sirolimus, potent CYP3A4 inducers, dabigatran **Important potential risk**	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3, 4.4 and 4.5.* – Prescription only medicine. Additional risk minimisation measures: *Education and reminder tool: Prescriber Guide*

Photosensitivity disorders and pigmentation disorders (extended to severe skin disorders) and neuropathy (including Optic Neuropathy) ***(Amiodarone-like effects)*** **Important potential risk**	
Risk minimisation measures	– Prescription only medicine. No minimization action is proposed as there is no evidence of such risks with the use of dronedarone.

Prolactin-induced mammary carcinogenesis (preclinical finding) **Important potential risk**	
Risk minimisation measures	– Prescription only medicine. No minimization action proposed, as not confirmed.

Effect in pregnancy **Missing information**

Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.6 and 5.3.* – Prescription only medicine. Additional risk minimisation measures: *None*

Effect in lactation **Missing information**	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6.* – Prescription only medicine. Additional risk minimisation measures: *None*

Effect in severe hepatic impairment **Missing information**	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2 and 4.3.* – Prescription only medicine. Additional risk minimisation measures: *Education and reminder tool: Prescriber Guide*

Effect in children (potential off-label use) **Missing information**	
Risk minimisation measures	Routine risk minimisation measures: *Section 4.2.* – Prescription only medicine. 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 dronedarone.

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

There are no studies required for dronedarone.