Summary of risk management plan for MULTAQ (Dronedarone)

This is a summary of the RMP for MULTAQ. The RMP details important risks of MULTAQ, how these risks can be minimized, and how more information will be obtained about MULTAQ's risks.

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

This summary of the RMP for MULTAQ should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

1. THE MEDICINE AND WHAT IT IS USED FOR

MULTAQ is authorized in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF) for the maintenance of sinus rhythm after successful cardioversion. Due to its safety profile, MULTAQ should only be prescribed after alternative treatment options have been considered.

MULTAQ must not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure (see SmPC for the full indication). It contains dronedarone as the active substance and it is given by oral route.

Further information about the evaluation of MULTAQ's benefits can be found in MULTAQ's EPAR, including in its plain-language summary, available on the European Medical Agency (EMA) website, under the medicine's webpage:

Refer to EPAR ref. European Medicines Agency (EMEA)/H/C/001043 -N/0040 dated 13 November 2017 available on the EMA website at the following link:

https://www.ema.europa.eu/documents/product-information/multaq-epar-product-information_en.pdf

2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of MULTAQ, together with measures to minimize such risks and the proposed studies for learning more about MULTAQ's risks, are outlined in the next sections.

Measures to minimize 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 authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of MULTAQ, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

2.1 List of important risks and missing information

Important risks of MULTAQ are risks that need special risk management activities to further investigate or minimize 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 MULTAQ. 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.

Table 1 - 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) Pulmonary - interstitial lung disease (ILD) Hepatotoxicity
Important potential risk	None
Missing information	None

AF: Atrial Fibrillation; ILD: Interstitial Lung Disease.

2.2 Summary of important risks

Table 2 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important identified risk: 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)

Important identified risk: 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)	
Evidence for linking the risk to the medicine	Clinical study reports: ANDROMEDA, pool of 5 placebo-controlled clinical studies in AF/AFL population, permanent AF/AFL study (PALLAS), DRI10939 study.
Risk factors and risk groups	The presence or absence of clinical stability was the primary feature that distinguished the patients enrolled in the ANDROMEDA and ATHENA trials. Both trials enrolled patients with low ejection fractions or with NYHA class II or III HF; however these patients had been hospitalized for worsening HF in the ANDROMEDA trial but were stable outpatients in the ATHENA trial. If the results of ANDROMEDA are considered reliable, this clinical instability defines the patients that should not receive dronedarone. Based on newly available data, patients with history of or current HF and LVSD are considered at risk.
Risk minimization measures	**Routine risk minimization measures**: SmPC: Labelled in sections 4.3, 4.4 and 4.8 Prescription only medicine **Additional risk minimization measures**: Tool for healthcare professionals: Prescriber guide

AF: Atrial Fibrillation; AFL: Atrial Flutter, HF: Heart Failure, LVSD: Left Ventricular Systolic Dysfunction, SmPC: Summary of Product Characteristics.

Table 3 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important identified risk: 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: 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)	
Evidence for linking the risk to the medicine	Postmarketing reports, PALLAS study, and epidemiology data.
Risk factors and risk groups	History of or current heart failure.
Risk minimization measures	**Routine risk minimization measures**: SmPC: Labelled in Section 4.3 and 4.4 Prescription only medicine

Important identified risk: 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)	
	Additional risk minimization measures: Tool for healthcare professionals: Prescriber guide

AF: Atrial Fibrillation; SmPC: Summary of Product Characteristics.

Table 4 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important identified risk: Pulmonary - interstitial lung disease

Important identified risk: Pulmonary - interstitial lung disease	
Evidence for linking the risk to the medicine	Postmarketing reports, clinical trials and epidemiology data.
Risk factors and risk groups	No specific risk factors have been determined other than a previous ILD reaction to amiodarone exposure.
Risk minimization measures	**Routine risk minimization measures**: SmPC: Labelled in sections 4.3, 4.4 and 4.8 Prescription only medicine **Additional risk minimization measures**: Tool for healthcare professionals: Prescriber guide

ILD: Interstitial Lung Disease, SmPC: Summary of Product Characteristics.

Table 5 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important identified risk: Hepatotoxicity

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Postmarketing reports, clinical trials and epidemiology data.
Risk factors and risk groups	In the Pool of 5 controlled clinical studies in AF/AFL population (DAFNE, EURIDIS, ADONIS, ERATO, ATHENA): additional post-hoc analyses on selected hepatic events showed a trend in which the dronedarone group had an earlier onset of hepatic AEs during the first 6 months compared to placebo. After 1 year, the incidences appeared to be similar in the 2 groups; data are entirely driven by AEs reported in the ATHENA study (enzymes not routinely collected). There was no interaction identified between treatment and baseline prognostic factors or medications for any specific hepatic events. <u>Postmarketing safety experience from launch until DLP:</u> Most of the severe cases of hepatocellular hepatotoxicity including hepatic failure appear to occur in the context of hypotension or reduced cardiac output. These cases occurred in the context of myocardial infarction, septic shock or worsening CHF. Many of these cases occurred within the first 30 days of dronedarone exposure.
Risk minimization measures	**Routine risk minimization measures**: SmPC: Labelled in sections 4.3, 4.4 and 4.8

Important identified risk: Hepatotoxicity	
	Prescription only medicine **Additional risk minimization measures**: Tool for healthcare professionals: Prescriber guide

AE: Adverse Event, AF: Atrial Fibrillation, AFL: Atrial Flutter, CHF: Congestive Heart Failure, DLP: Data Lock Point; SmPC: Summary of Product Characteristics.

2.3 Post-authorization development plan

2.3.1 Studies which are conditions of the marketing authorization

There is no study which is condition of the marketing authorization or specific obligation of dronedarone.

2.3.2. Other studies in post-authorization development plan

There is no study required for dronedarone.