Summary of risk management plan for BRINAVESS (vernakalant hydrochloride)

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

BRINAVESS's SmPC and its package leaflet (PL) give essential information to HCPs and patients on how BRINAVESS should be used.

This summary of the RMP for BRINAVESS 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 BRINAVESS's RMP.

I. The medicine and what it is used for

BRINAVESS is authorised for rapid conversion of recent onset atrial fibrillation to SR in adults for non-surgery patients with atrial fibrillation ≤ 7 days duration and for post-cardiac surgery patients with atrial fibrillation ≤ 3 days duration. It contains vernakalant hydrochloride as the active substance and it is given by concentrate for solution for infusion, 20 mg/ml.

Further information about the evaluation of BRINAVESS's benefits can be found in BRINAVESS's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

Important risks of BRINAVESS, together with measures to minimise such risks and the proposed studies for learning more about BRINAVESS'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 PL and SmPC addressed to patients and HCPs;
- 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 BRINAVESS, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about ADRs is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. BRINAVESS is not widely prescribed and used only in an hospital setting by well qualified

HCPs with continuous monitoring. These measures constitute routine pharmacovigilance activities.

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

II.A List of important risks and missing information

Important risks of BRINAVESS 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 BRINAVESS. 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).

Table 1 List of important risks and missing information

Important identified risks	Hypotension Bradycardia Atrial flutter ECG QRS complex prolonged Ventricular arrhythmia in patients with history of valvular heart disease Ventricular arrhythmia in patients with history/evidence of congestive heart failure
Important potential risks	Overdose/medication error
Missing information	Patients with heart failure NYHA Class III and IV Patients with prolonged QT (uncorrected >440msec) Patients with severe bradycardia and second or third degree block Patients with clinically meaningful valvular stenosis Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constructive pericarditis Use of PO antiarrhythmic therapy (Class I and III)

	Hepatic impairment Off label use including: severe aortic stenosis, or systolic BP<100mmHg patients with recent MI or ACS, patients treated for arrhythmias other than AF, use of IV AAD (Class I and Class III) within 4hours prior to vernakalant administration and within the first 4hours after vernakalant administration

II.B Summary of important risks

Table 2 Summary of important identified risk of hypotension

Identified risk: Hypotension	
Evidence for linking the risk to the medicine	Clinical trial data (BRINAVESS™ CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO Clinical Study Report [CSR]; ACT V CSR); published information on other anti- arrhythmic products; postmarketing AE report data [company PV database [Worldwide Adverse Experience System, WAES]), integrated safety analysis.
Risk factors and risk groups	Clinical trial experience has identified populations at increased risk of hypotension: • Haemodynamically unstable patients • Patients with history of CHF
Risk minimisation measures	<u>Routine risk communication:</u> SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 4.2, 4.3 4.4 No other routine risk minimisation measures beyond the PI <u>Additional risk minimisation measures</u> HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 3 Summary of important identified risk of bradycardia

Identified risk: Bradycardia	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™ SmPC; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES), integrated safety analysis.
Risk factors and risk groups	Conversion from AF to SR; patients with known bradycardia or sick sinus syndrome unless controlled by a pacemaker. In patients with a history of VHD, bradycardia events occurred more frequently in the subgroup of patients treated with vernakalant, compared to those treated with PBO.
Risk minimisation measures	<u>Routine risk communication:</u> SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 4.2, 4.3, 4.4 No other routine risk minimisation measures beyond the PI <u>Additional risk minimisation measures</u> HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 4 Summary of important identified risk of atrial flutter

Identified risk: Atrial flutter	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™ CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES)], integrated safety analysis.
Risk factors and risk groups	Class I antiarrhythmics, increase the risk of AFL
Risk minimisation measures	<u>Routine risk communication:</u> SmPC sections 4.2, 4.4, and 4.8 PL sections 4.2, 4.4

Identified risk: Atrial flutter	
	No other routine risk minimisation measures beyond the PI <u>Additional risk minimisation measures</u> HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 5 Summary of important identified risk of ECG QRS complex prolonged

Identified risk: ECG QRS complex prolonged	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™ CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); ACT IV CSR; AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES), integrated safety analysis.
Risk factors and risk groups	Patients with known myocardial disease, background use of Class I antiarrhythmics, CHF, LV dysfunction or high ventricular rate.
Risk minimisation measures	<u>Routine risk communication:</u> SmPC sections 4.4, and 4.8 PL sections 4.4 No other routine risk minimisation measures beyond the PI <u>Additional risk minimisation measures</u> HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 6 Summary of important identified risk of ventricular arrhythmia in patients with history of valvular heart disease

Identified risk: Ventricular arrhythmia in patients with history of valvular heart disease	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES), integrated safety analysis.
Risk factors and risk groups	In patients with a history of VHD, VA events occurred more frequently in the subgroup of patients treated with vernakalant, compared to those treated with PBO.
Risk minimisation measures	Routine risk communication: SmPC sections 4.3, 4.4, and 4.8 PL sections 4.3, 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 72 Summary of important identified risk of ventricular arrhythmia in patients with history/evidence of congestive heart failure

Identified risk: Ventricular arrhythmia in patients with history/evidence of congestive heart failure	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES), integrated safety analysis.
Risk factors and risk groups	In patients with a history of CHF events occurred more frequently in the subgroup of patients treated with vernakalant, compared to those treated with PBO.

Identified risk: Ventricular arrhythmia in patients with history/evidence of congestive heart failure	
Risk minimisation measures	Routine risk communication: SmPC sections 4.3, 4.4, and 4.8 PL sections 4.3, 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 8 Summary of important potential risk of overdose/medication error

Important Potential risk: Overdose/medication error	
Evidence for linking the risk to the medicine	Clinical trial data [BRINAVESS™ CCDS; Marketing Application Subsections 2.5 (Clinical Overview) and 2.7.4 (Summary of Clinical Safety); AVRO CSR; ACT V CSR]; published information on other anti-arrhythmic products; postmarketing AE report data [company PV database (WAES), integrated safety analysis.
Risk factors and risk groups	No risk groups or risk factors have been identified.
Risk minimisation measures	Routine risk communication: SmPC sections 4.2 and 4.9 PL sections 4.2 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 9 Summary of missing information of patients with heart failure NYHA Class III and IV

Missing information: Patients with heart failure NYHA Class III and IV	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3 PL sections 4.3 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 10 Summary of missing information of patients with prolonged QT (uncorrected >440 msec)

Missing information: Patients with prolonged QT (uncorrected >440msec)	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3 PL sections 4.3 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 11 Summary of missing information of patients with severe bradycardia and second or third degree heart block

Missing information: Patients with severe bradycardia and second or third degree block	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3, 4.4 PL sections 4.3, 4.4 No other routine risk minimisation measures beyond the PI

Missing information: Patients with severe bradycardia and second or third degree block	
	Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 12 Summary of missing information of patients with clinically meaningful valvular stenosis

Missing information: Patients with clinically meaningful valvular stenosis	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 PL sections 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 13 Summary of missing information of patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy or constructive pericarditis

Missing information: Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constructive pericarditis	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 PL sections 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 14 Summary of missing information of use of PO antiarrhythmic therapy (Class I and III)

Missing information: Use of PO antiarrhythmic therapy (Class I and III)	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 PL sections 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table Summary of missing information of hepatic impairment

Missing information: Hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 PL sections 4.4 No other routine risk minimisation measures beyond the PI Additional risk minimisation measures HCP education materials: HCP Education Card and Pre-Infusion checklist.

Table 15 Summary of missing information of off label use

Missing information: Off label use including: severe aortic stenosis, or systolic BP<100mmHg, Patients with recent MI or ACS, patients treated for arrhythmias other than AF, Use of IV AAD (Class I and Class III) within 4hours prior to vernakalant administration and within the first 4hours after vernakalant administration	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3 PL sections 4.3 No other routine risk minimisation measures beyond the PI

Missing information: Off label use including: severe aortic stenosis, or systolic BP<100mmHg, Patients with recent MI or ACS, patients treated for arrhythmias other than AF, Use of IV AAD (Class I and Class III) within 4hours prior to vernakalant administration and within the first 4hours after vernakalant administration	
	<u>Additional risk minimisation measures</u> HCP education materials: HCP Education Card and Pre-Infusion checklist.

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 BRINAVESS.

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

There are no studies required for BRINAVESS