ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BRINAVESS 20 mg/ml, concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 20 mg of vernakalant hydrochloride which is equivalent to 18.1 mg of vernakalant free base.

Each 10 ml vial of 200 mg of vernakalant hydrochloride is equivalent to 181 mg of vernakalant free base.
Each 25 ml vial of 500 mg of vernakalant hydrochloride is equivalent to 452.5 mg of vernakalant free base.

After dilution the concentration of the solution is 4 mg/ml vernakalant hydrochloride

Excipient: Each vial of 200 mg contains approximately 1.4 mmol (32 mg) sodium. Each vial of 500 mg contains approximately 3.5 mmol (80 mg) of sodium.

Each administered millilitre of the diluted solution contains approximately 3.5 mg of sodium (sodium chloride 9 mg/ml (0.9%) solution for injection), 0.64 mg sodium (Glucose injection 5%) or 3.2 mg sodium (Lactated Ringers for Injection).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).
Clear and colourless to pale yellow solution with a pH of approximately 5.5.

The osmolality of the medicinal product is controlled between the following range:
270-320 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults
-For non-surgery patients: atrial fibrillation ≤ 7 days duration
-For post-cardiac surgery patients: atrial fibrillation ≤ 3 days duration

4.2 Posology and method of administration

BRINAVESS should be administered by intravenous infusion, by qualified medical personnel in a monitored clinical setting appropriate for cardioversion.

Posology
BRINAVESS is dosed by patient body weight, with a maximum calculated dose based upon 113 kgs. The recommended initial infusion is 3 mg/kg to be infused over a 10 minute period. For patients weighing ≥ 113 kg, do not exceed the maximum initial dose of 339 mg (84.7 ml of 4 mg/ml solution). If conversion to sinus rhythm does not occur within 15 minutes after the end of the initial infusion, a second 10 minute infusion of 2 mg/kg may be administered. For patients weighing ≥ 113 kg, do not exceed the maximum second infusion of 226 mg (56.5 ml of 4 mg/ml solution). Cumulative doses of greater than 5 mg/kg should not be administered within 24 hours. There are no clinical data on repeat

doses after the initial and second infusions. By 24 hours there appears to be insignificant levels of vernakalant.

If conversion to sinus rhythm occurs during either the initial or second infusion, that infusion should be continued to completion. If haemodynamically stable atrial flutter is observed after the initial infusion, the second infusion of BRINAVESS may be administered as patients may convert to sinus rhythm. (See sections 4.4 and 4.8.)

An infusion pump is the preferred delivery device. However, a syringe pump is acceptable provided that the calculated volume can be accurately given within the specified infusion time.

Do not administer as an intravenous push or bolus.

Recommended diluents are 0.9% Sodium Chloride for Injection, Lactated Ringers for Injection, or 5% Glucose for Injection.

Read all steps before administration.

Preparation of BRINAVESS for infusion
Step 1: Visually inspect BRINAVESS vials for particulate matter and discolouration before administration. Do not use any vials exhibiting particulate matter or discolouration. Note: BRINAVESS concentrate for solution for infusion ranges from colourless to pale yellow. Variations of colour within this range do not affect potency.

Step 2: Dilution of concentrate
To ensure proper administration, a sufficient amount of BRINAVESS 20 mg/ml should be prepared at the outset of therapy to deliver the initial and second infusion should it be warranted.
Create a solution with a concentration of 4mg/ml following the dilution guidelines below:
Patients ≤ 100 kg: 25 ml of BRINAVESS 20 mg/ml is added to 100 ml of diluent.
Patients > 100 kg: 30 ml of BRINAVESS 20 mg/ml is added to 120 ml of diluent.

Step 3: Inspect solution
The diluted sterile solution should be clear, colourless to pale yellow. Visually re-inspect the solution for particulate matter and discolouration before administering.

Method of administration
BRINAVESS vials are for single use only and must be diluted prior to administration.

Step 4: Administration of the initial infusion
The initial infusion of BRINAVESS is administered as a 3 mg/kg dose over 10 minutes.

Step 5: Patient observation
If conversion to sinus rhythm has not occurred, observe the patient's vital signs and cardiac rhythm for an additional 15 minutes.

Step 6: Administration of second infusion
If conversion to sinus rhythm did not occur with the initial infusion or within the 15 minute observation period, administer a 2 mg/kg second infusion over 10 minutes.

Cumulative doses above 565 mg have not been evaluated.

Post-cardiac surgery patients:
No dose adjustment necessary.

Renal impairment:
No dose adjustment necessary (see section 5.2).

Hepatic impairment:
No dose adjustment necessary (see sections 4.4 and 5.2).

Elderly (≥ 65 years):
No dose adjustment necessary.

*Paediatric population**:***
There is no relevant use of BRINAVESS in children and adolescents < 18 years of age in the current indication and therefore should not be used in this population.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see section 6.1).
- Patients with severe aortic stenosis, patients with systolic blood pressure <100 mm Hg, and patients with heart failure class NYHA III and NYHA IV.
- Patients with prolonged QT at baseline (uncorrected > 440 msec), or severe bradycardia, sinus node dysfunction or second degree and third degree heart block in the absence of a pacemaker.
- Use of intravenous rhythm control anti-arrhythmics (class I and class III) within 4 hours prior to BRINAVESS administration.
- Acute coronary syndrome (including myocardial infarction) within the last 30 days.

4.4 Special warnings and precautions for use

Patients should be observed with assessment of vital signs and continuous cardiac rhythm monitoring during and after administration of BRINAVESS, until clinical and ECG parameters have stabilised.

Direct-current cardioversion may be considered for patients who do not respond to therapy. There is no clinical experience with direct-current cardioversion under two hours postdose.

Prior to attempting pharmacological cardioversion, ensure that patients are adequately hydrated and haemodynamically optimized and if necessary patients should be anticoagulated in accordance with treatment guidelines. In patients with uncorrected hypokalemia (serum potassium of less than 3.5 mmol/l), potassium levels should be corrected prior to use of BRINAVESS.

During infusion of BRINAVESS, if patients develop clinically meaningful bradycardia and/or hypotension or develop ECG changes (such as a clinically meaningful sinus pause, complete heart block, new bundle branch block, significant prolongation of the QRS or QT interval, changes consistent with ischaemia or infarction and ventricular arrhythmia), the administration of BRINAVESS should be discontinued and these patients should receive appropriate medical management. If these events occur during the first infusion of BRINAVESS, patients should not receive the second dose of BRINAVESS.

<u>Hypotension</u>
Hypotension can occur in a small number of patients (vernakalant 7.6%, placebo 5.1%). Hypotension typically occurs early, either during the infusion or early after the end of the infusion, and can usually be corrected by standard supportive measures. Patients with congestive heart failure (CHF) have been identified as a population at higher risk for hypotension. (See section 4.8.)

<u>Congestive Heart Failure</u>
Patients with CHF showed a higher overall incidence of hypotensive events, during the first 2 hours after dose in patients treated with vernakalant compared to patients receiving placebo (16.1% versus 4.7%, respectively). In patients without CHF the incidence of hypotension was not significantly different during the first 2 hours after dose in patients treated with vernakalant compared to patients receiving placebo (5.7% versus. 5.2%, respectively). Hypotension reported as a serious adverse experience or leading to medicine discontinuation occurred in CHF patients following exposure to BRINAVESS in 2.9% of these patients compared to 0% in placebo.

Patients with a history of CHF showed a higher incidence of ventricular arrhythmia in the first two hours post dose (7.3% for BRINAVESS compared to 1.6% in placebo). These arrhythmias typically presented as asymptomatic, monomorphic, non-sustained (average 3-4 beats) ventricular tachycardias. By contrast, ventricular arrhythmias were reported with similar frequencies in patients without a history of CHF who were treated with either BRINAVESS or placebo (3.2% for BRINAVESS versus 3.6% for placebo).

Due to the higher incidence of the adverse events of hypotension and ventricular arrhythmia in patients with CHF, vernakalant should be used cautiously in haemodynamically stable patients with CHF functional classes NYHA I to II. There is limited experience with the use of vernakalant in patients with previously documented LVEF $\leq$ 35%. its use in these patients is not recommended. The use in CHF patients corresponding to NYHA III or NYHA IV is contraindicated (see section 4.3).

Atrial Flutter
BRINAVESS was not found to be effective in converting typical primary atrial flutter to sinus rhythm. Patients receiving BRINAVESS have a higher incidence of converting to atrial flutter within the first 2 hours post-dose. This risk is higher in patients who use Class I antiarrhythmics (see section 4.8). If atrial flutter is observed as secondary to treatment, continuation of infusion should be considered (see section 4.2)

Use of AADs (anti-arrhythmic drugs) prior to or after BRINAVESS
BRINAVESS can not be recommended in patients previously administered intravenous AADs (class I and III) 4-24 hours prior to vernakalant due to lack of data. BRINAVESS should not be administered in patients who received intravenous AADs (class I and III) within 4 hours prior to vernakalant (see section 4.3).

BRINAVESS should be used with caution in patients on oral AADs (class I and III), due to limited experience. Risk of atrial flutter may be increased in patients receiving class I AADs (see above).

There is limited experience with the use of intravenous rhythm control anti-arrhythmics (class I and class III) in the first 4 hours after BRINAVESS administration, therefore these agents should be used cautiously within this period. Resumption or initiation of oral maintenance antiarrhythmic therapy can be considered starting 2 hours after vernakalant administration.

Valvular Heart Disease
In patients with valvular heart disease, there was a higher incidence of ventricular arrhythmia events in vernakalant patients. These patients should be monitored closely.

Other Diseases and Conditions not Studied
BRINAVESS has been administered to patients with an uncorrected QT less than 440 msec without an increased risk of torsade de pointes.

Furthermore, BRINAVESS has not been evaluated in patients with clinically meaningful valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis and its use can not be recommended in such cases. There is limited experience with BRINAVESS in patients with pacemakers.

As the clinical trial experience in patients with advanced hepatic impairment is limited, vernakalant is not recommended in these patients.

This medicinal product contains approximately 1.4 mmol (32 mg) sodium in each 200 mg vial. Each vial of 500 mg contains approximately 3.5 mmol (80 mg) of sodium.
This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been undertaken with vernakalant injection. Within the clinical development program, oral maintenance antiarrhythmic therapy was halted for a minimum of 2 hours after BRINAVESS administration. Resumption or initiation of oral maintenance antiarrhythmic therapy after this time period can be considered (see sections 4.3 and 4.4).

Although vernakalant is a substrate of CYP2D6, population pharmacokinetic (PK) analyses demonstrated that no substantial differences in the acute exposure of vernakalant (Cmax and AUC0-90min) were observed when weak or potent CYP2D6 inhibitors were administered within 1 day prior to vernakalant infusion compared to patients that were not on concomitant therapy with CYP2D6 inhibitors. In addition, acute exposure of vernakalant in poor metabolisers of CYP2D6 is only minimally different when compared to that of extensive metabolisers. No dose adjustment of vernakalant is required on the basis of CYP2D6 metaboliser status, or when vernakalant is administered concurrently with 2D6 inhibitors.

Vernakalant is a moderate, competitive inhibitor of CYP2D6. However, acute intravenous administration of vernakalant is not expected to markedly impact the PK of chronically administered 2D6 substrates, as a consequence of vernakalant's short half life and the ensuing transient nature of 2D6 inhibition. Vernakalant given by infusion is not expected to perpetrate meaningful drug interactions due to the rapid distribution and transient exposure, low protein binding, lack of inhibition of other CYP P450 enzymes tested (CYP3A4, 1A2, 2C9, 2C19 or 2E1) and lack of P-glycoprotein inhibition in a digoxin transport assay.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of vernakalant hydrochloride in pregnant women. Animal studies have shown malformations after repeated oral exposure (see section 5.3). As a precautionary measure, it is preferable to avoid the use of vernakalant during pregnancy.

Breast-feeding
It is unknown whether vernakalant/metabolites are excreted in human milk.
There is no information on the excretion of vernakalant/metabolites in animal milk.
A risk to the suckling child cannot be excluded.
Caution should be exercised when used in breastfeeding women.

Fertility
Vernakalant was not shown to alter fertility in animal studies.

4.7 Effects on ability to drive and use machines

No studies on the effects of BRINAVESS on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines, it should be taken into account that, dizziness has been reported within the first two hours after taking BRINAVESS (see section 4.8).

4.8 Undesirable effects

The safety of BRINAVESS has been evaluated in clinical studies involving 883 subjects (patients and healthy volunteers) who received treatment with BRINAVESS. Based on data from 773 patients in six phase 2 and phase 3 trials, the most commonly reported adverse reactions (> 5%) seen in the first 24 hours after receiving BRINAVESS were dysgeusia (taste disturbance) (20.1%), sneezing (14.6%) and paraesthesia (9.7%). These events occurred around the time of infusion, were transient and were rarely treatment limiting.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000), not known (cannot be estimated from the available data)

Table1:
Adverse reactions with BRINAVESS *

Nervous system disorders	*Very common:* Dysgeusia *Common:* Paraesthesia, dizziness, headache, hypoaesthesia *Uncommon:* Burning sensation, parosmia, somnolence, vasovagal syncope
Eye disorders	*Uncommon:* Eye irritation, lacrimation increased, visual disturbance
Cardiac disorders	*Common:* Bradycardia**, atrial flutter** *Uncommon*: Sinus arrest, complete AV block, first degree AV block, left bundle branch block, ventricular extrasystoles, palpitations, sinus bradycardia, ventricular tachycardia, ECG QRS complex prolonged, ECG QT prolonged
Vascular disorders	*Common:* Hypotension *Uncommon:* Flushing, hot flush, pallor
Respiratory, thoracic and mediastinal disorders	*Very common:* Sneezing *Common:* Cough, nasal discomfort *Uncommon:* Dyspnoea, suffocation feeling, rhinorrhoea, throat irritation
Gastrointestinal disorders	*Common:* Nausea, vomiting, dry mouth *Uncommon:* Diarrhoea, defecation urgency
Skin and subcutaneous tissue disorders	*Common:* Pruritus, hyperhidrosis *Uncommon:* Generalised pruritis, cold sweat
Musculoskeletal and connective tissue disorders	*Uncommon:* Pain in extremity
General disorders and administrative site conditions	*Common:* Infusion site pain, infusion site paraesthesia, feeling hot, fatigue *Uncommon:* Infusion site irritation, infusion site hypersensitivity, malaise, chest discomfort

* The adverse reactions included in the table occurred within 24 hours of administration of BRINAVESS (see sections 4.2 and 5.2)
**see section below

Description of selected adverse reactions:
Clinically significant adverse reactions observed in clinical trials included hypotension and ventricular arrhythmia. (See sections 4.4 Hypotension, Congestive Heart Failure).

Bradycardia was observed predominantly at the time of conversion to sinus rhythm. With a significantly higher conversion rate in patients treated with BRINAVESS, the incidence of bradycardia events was higher within the first 2 hours in vernakalant treated patients than in placebo-treated patients (5.4% versus 3.8%, respectively). Of the patients who did not convert to sinus rhythm, the incidence of bradycardia events in the first 2 hours postdose was similar in placebo and vernakalant treated groups (4.0% and 3.8%, respectively). In general, bradycardia responded well to discontinuation of BRINAVESS and/or administration of atropine.

Atrial Flutter
Atrial fibrillation patients receiving BRINAVESS have a higher incidence of converting to atrial flutter within the first 2 hours postdose (10% versus 2.5% in placebo). With continuation of the medicine infusion as recommended above, the majority of these patients continue to convert to sinus rhythm. In the remaining patients, electrical cardioversion can be recommended. In clinical studies to date, patients who developed atrial flutter following treatment with BRINAVESS did not develop 1:1 atrioventricular conduction.

AVRO Study
In a clinical trial involving 116 patients with recent onset atrial fibrillation who received BRINAVESS, the observed adverse experience profile appeared to be consistent with that reported in the prior trials.

4.9 Overdose

No case of overdose with BRINAVESS has been reported in clinical trials. One patient who received 3 mg/kg of BRINAVESS over 5 minutes (instead of the recommended 10 minutes) developed haemodynamically stable wide complex tachycardia which resolved without sequelae.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, other antiarrhythmics class I and III, ATC code: C01BG11.

Mechanism of Action: Vernakalant is an antiarrhythmic medicine that acts preferentially in the atria to prolong atrial refractoriness and to rate-dependently slow impulse conduction. These anti-fibrillatory actions on refractoriness and conduction are thought to suppress re-entry, and are potentiated in the atria during atrial fibrillation. The relative selectivity of vernakalant on atrial versus ventricular refractoriness is postulated to result from the block of currents that are expressed in the atria, but not in the ventricles, as well as the unique electrophysiologic condition of the fibrillating atria. However, blockade of cationic currents, including hERG channels and cardiac voltage-dependent sodium channels, which are present in the ventricles has been documented.

Pharmacodynamics: In preclinical studies, vernakalant blocks currents in all phases of the atrial action potential, including potassium currents that are expressed specifically in the atria (e.g., the ultra-rapid delayed rectifier and the acetylcholine dependent potassium currents). During atrial fibrillation, the frequency- and voltage-dependent block of sodium channels further focuses the action of the medicine toward rapidly activating and partially depolarized atrial tissue rather than toward the normally polarized ventricle beating at lower heart rates. Additionally, the ability of vernakalant to block the late component of the sodium current limits effects on ventricular repolarisation induced by blockade of potassium currents in the ventricle. Targeted effects on atrial tissue coupled with block of late sodium current suggests that vernakalant has a low proarrhythmic potential. Overall, the combination of effects of vernakalant on cardiac potassium and sodium currents results in substantial antiarrhythmic effects that are mainly concentrated in the atria.

In an electrophysiological study in patients, vernakalant significantly prolonged atrial effective refractory period in a dose-dependent manner, which was not associated with a significant increase in ventricular effective refractory period. Across the Phase 3 population, vernakalant treated patients had an increase in heart rate-corrected QT (using Fridericia's correction, QTcF) compared to placebo (22.1 msec and 18.8 msec placebo-subtracted peaks after first and second infusions, respectively). By 90 minutes after the start of infusion, this difference was reduced to 8.1 msec.

Clinical efficacy

Clinical Trial Design: The clinical effect of BRINAVESS in the treatment of patients with atrial fibrillation has been evaluated in three, randomised, double-blind, placebo-controlled studies, (ACT I, ACT II and ACT III) and in an active comparator trial versus intravenous amiodarone (AVRO). Some patients with typical atrial flutter were included in ACT II and ACT III and BRINAVESS was not found to be effective in converting atrial flutter. In clinical studies, the need for anticoagulation prior to administration of vernakalant was assessed as per clinical practice of the treating physician. For atrial fibrillation lasting less than 48 hours, immediate cardioversion was allowed. For atrial fibrillation lasting longer than 48 hours, anticoagulation was required as per treatment guidelines.

ACT I and ACT III studied the effect of BRINAVESS in the treatment of patients with sustained atrial fibrillation > 3 hours but not more than 45 days in duration. ACT II examined the effect of BRINAVESS on patients who developed atrial fibrillation of < 3 days duration after recently undergoing coronary artery bypass graft, (CABG) and/or valvular surgery (atrial fibrillation occurred more than 1 day but less than 7 days after surgery). AVRO studied the effect of vernakalant versus intravenous amiodarone in patients with recent onset atrial fibrillation (3 hrs to 48 hrs). In all studies, patients received a 10-minute infusion of 3.0 mg/kg BRINAVESS (or matching placebo) followed by a 15-minute observation period. If the patient was in atrial fibrillation or atrial flutter at the end of the 15-minute observation period, a second 10-minute infusion of 2.0 mg/kg BRINAVESS (or matching placebo) was administered. Treatment success (responder) was defined as conversion of atrial fibrillation to sinus rhythm within 90 minutes. Patients who did not respond to treatment were managed by the physician using standard care.

Efficacy in patients with sustained atrial fibrillation, (ACT I and ACT III)

Primary efficacy endpoint was the proportion of subjects with short duration atrial fibrillation (3 hours to 7 days) who had a treatment-induced conversion of atrial fibrillation to sinus rhythm for a minimum duration of one minute within 90 minutes of first exposure to study drug. Efficacy was studied in a total of 390 haemodynamically stable adult patients with short duration atrial fibrillation including patients with hypertension (40.5%), ischaemic heart disease (12.8%), valvular heart disease (9.2%) and CHF (10.8%). In these studies treatment with BRINAVESS effectively converted atrial fibrillation to sinus rhythm as compared with placebo (see Table 2). Conversion of atrial fibrillation to sinus rhythm occurred rapidly (in responders the median time to conversion was 10 minutes from start of first infusion) and sinus rhythm was maintained through 24 hours (97%). The vernakalant dose recommendation is a titrated therapy with two possible dose steps. In the performed clinical studies, the additive effect of the second dose, if any, can not be independently established.

Table 2: Conversion of Atrial Fibrillation to Sinus Rhythm in ACT I and ACT III

Duration of Atrial Fibrillation	**ACT I**			**ACT III**		
	BRINAVESS	**Placebo**	**P-Value†**	**BRINAVESS**	**Placebo**	**P-Value†**
> 3 hours to ≤ 7 days	74/145 (51.0%)	3/75 (4.0%)	< 0.0001	44/86 (51.2%)	3/84 (3.6%)	< 0.0001

†Cochran-Mantel-Haenszel test

BRINAVESS was shown to provide relief of atrial fibrillation symptoms consistent with conversion to sinus rhythm.

No significant differences in safety or effectiveness were observed based on age, gender, use of rate control medications, use of antiarrhythmic medications, use of warfarin, history of ischaemic heart disease, renal impairment or expression of the cytochrome P450 2D6 enzyme.

Treatment with BRINAVESS did not affect the response rate to electrical cardioversion (including the median number of shocks or joules required for successful cardioversion) in cases when attempted within 2 to 24 hours of study medicine administration.

Conversion of atrial fibrillation in patients with longer-duration atrial fibrillation (> 7 days and ≤ 45 days) assessed as a secondary efficacy endpoint in a total of 185 patients did not show statistically significant differences between BRINAVESS and placebo.

Efficacy in patients who developed atrial fibrillation post cardiac surgery (ACT II)
Efficacy was studied in patients with atrial fibrillation after cardiac surgery in ACT II, a phase 3, double-blind, placebo-controlled, parallel group study (ACT II) in 150 patients with sustained atrial fibrillation (3 hours to 72 hours duration) that occurred between 24 hours and 7 days post coronary artery bypass graft and/or valvular surgery. Treatment with BRINAVESS effectively converted atrial fibrillation to sinus rhythm (47.0% BRINAVESS, 14.0% placebo; P value = 0.0001). Conversion of atrial fibrillation to sinus rhythm occurred rapidly (median time to conversion 12 minutes from the start of infusion).

Efficacy versus amiodarone (AVRO):
Vernakalant was studied in 116 pts with atrial fibrillation (3 hrs to 48 hrs) including patients with hypertension (74.1%), IHD (19%), valvular heart disease (3.4%) and CHF (17.2%). No patients with NYHA III/IV were included in the study. In AVRO, the amiodarone infusion was given over 2 hours (i.e., 1 hour loading dose of 5 mg/kg, followed by 1 hour maintenance infusion of 50 mg). The primary endpoint was the proportion of patients that achieved sinus rhythm (SR) at 90 minutes after initiating therapy, limiting the conclusions to the effects seen in this time window. Treatment with vernakalant, converted 51.7% of patients to SR at 90 minutes versus 5.2% with amiodarone resulting in a significantly faster conversion rate from AF to SR within the first 90 minutes compared to amiodarone (log-rank P-value < 0.0001).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with BRINAVESS in all subsets of the paediatric population in atrial fibrillation (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
In patients, average peak plasma concentrations of vernakalant were 3.9 μg/ml following a single 10 minute infusion of 3 mg/kg vernakalant hydrochloride, and 4.3 μg/ml following a second infusion of 2 mg/kg with a 15 minute interval between doses.

Distribution
Vernakalant is extensively and rapidly distributed in the body, with a volume of distribution of approximately 2 l/kg. The Cmax and AUC were dose proportional between 0.5 mg/kg and 5 mg/kg. In patients, the typical total body clearance of vernakalant was estimated to be 0.41 l/hr/kg. The free fraction of vernakalant in human serum is 53-63% at concentration range of 1-5 μg/ml.

Elimination/excretion
Vernakalant is mainly eliminated by CYP2D6 mediated O-demethylation in CYP2D6 extensive metabolisers. Glucuronidation and renal excretion are the main mechanisms of elimination in CYP2D6 poor metabolisers. The mean elimination half life of vernakalant in patients was approximately 3 hours in CYP2D6 extensive metabolisers and approximately 5.5 hours in poor metabolisers.

Special patient groups
Acute exposure is not significantly influenced by gender, history of congestive heart failure, renal impairment, or concomitant administration of beta blockers and other medications, including warfarin, metoprolol, furosemide and digoxin. In patients with hepatic impairment, exposures were elevated by 9 to 25%. No dose adjustment of BRINAVESS is required for these conditions, nor on the basis of age, serum creatinine or CYP2D6 metaboliser status.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, single- and repeated-dose toxicity, and genotoxicity.

With respect to reproduction no effects on pregnancy, embryofetal development, parturition or postnatal development were observed after intravenous administration of vernakalant at exposure levels (AUC) similar or below the human exposure levels (AUC) achieved after a single intravenous dose of vernakalant. In embryofetal development studies with oral administration of vernakalant two times a day resulting in exposure levels (AUC) generally higher than those achieved in humans after a single intravenous dose of vernakalant malformations (misshapen/absent/fused skull bones including cleft palates, bent radius, bent/misshapen scapula, constricted trachea, absent thyroid, undescendent testes) occurred in rats and increased embryofetal lethality, increased number of fetuses with fused and/or additional sternebrae were seen in rabbits at the highest doses tested.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid E330
Sodium chloride
Water for injection
Sodium hydroxide E524 (for pH-adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

3 years

The diluted sterile concentrate is chemically and physically stable for 12 hours at or below 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Single-use glass (Type 1) vials with a chlorobutyl rubber stopper and an aluminium overseal. Pack size of 1 vial includes either a 10 ml solution of 200 mg or a 25 ml solution of 500 mg.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

See section 4.2 for Preparation of BRINAVESS for infusion.

Any unused product or waste material should be disposed of in accordance with local requirements. BRINAVESS does not contain a preservative.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

<Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/>

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
NL-2031 BN Haarlem
The Netherlands

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **Conditions or restrictions regarding supply and use imposed on the marketing authorisation holder**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- **Conditions or restrictions with regard to the safe and effective use of the medicinal product**

The Marketing Authorisation Holder shall ensure that all Healthcare Professionals (HCP) involved in the administration of BRINAVESS are provided with a healthcare professional information pack containing the following:

Educational material for Healthcare Professionals
Summary of Product Characteristics, Package Leaflet and Labelling

Key elements to be included in the educational material:

1. BRINAVESS should be administered by intravenous infusion, by qualified medical personnel in a monitored clinical setting appropriate for cardioversion.

2. Appropriate measures to manage and minimize the risks, including the need for close monitoring during and after administration of BRINAVESS.

3. Patient selection criteria, including contraindications, special warnings and precautions for use and information about patient populations with limited information from clinical trials.

- Alert HCP on BRINAVESS contraindications:
    - Patients with prolonged QT at baseline (uncorrected > 440 msec), or severe bradycardia, sinus node dysfunction or second degree and third degree heart block in the absence of a pacemaker.
    - Use of intravenous rhythm control anti-arrhythmics (class I and class III) within 4 hours prior to BRINAVESS administration.
    - Acute coronary syndrome (including myocardial infarction) within the last 30 days
    - Patients with severe aortic stenosis, patients with systolic blood pressure <100 mm Hg, and patients with heart failure class NYHA III and NYHA IV.

- Alert HCP about BRINAVESS special warnings and precautions in patients with, clinically meaningful valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis, previously documented LVEF ≤ 35%, advanced hepatic impairment.
- Alert HCP about the need of precautions when using BRINAVESS in haemodynamically stable patients with congestive heart failure NYHA I and NYHA II and the need to monitor patients with valvular heart disease closely.

- Alert HCP for adverse events, which may occur after BRINAVESS administration, including hypotension, bradycardia, atrial flutter, or ventricular arrhythmia.
- Alert HCP for use of AADs (anti-arrhythmic drugs) prior to or after BRINAVESS.
    - BRINAVESS can not be recommended in patients previously administered intravenous AADs (class I and III) 4-24 hours prior to vernakalant, due to lack of data.
    - BRINAVESS should be used with caution in patients on oral AADs (class I and III), due to limited experience. Risk of atrial flutter may be increased in patients receiving class I AADs.,
    - Resumption or initiation of oral-maintenance antiarrhythmic therapy can be considered 2 hours after BRINAVESS administration.
    - Intravenous rhythm control AADs should be used cautiously in the first 4 hours after BRINAVESS administration.

4. Instructions on dose calculation, preparation of the solution for infusion, and method of administration.

5. BRINAVESS may be available in different vial sizes [available vial sizes to be inserted locally]. The number of vials of BRINAVESS concentrate required to prepare the appropriate quantity of solution for the treatment of an individual patient will depend on the patient's weight, and the vial size.

- **Other conditions**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 6 (22nd June 2009) presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.3 (23 June 2010) of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.
As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
At the request of the EMEA .

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR THE 10 ML VIAL

1. NAME OF THE MEDICINAL PRODUCT

BRINAVESS 20 mg/ml concentrate for solution for infusion
vernakalant hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 10 ml vial contains 200 mg vernakalant hydrochloride equivalent to 181 mg vernakalant free base.

3. LIST OF EXCIPIENTS

Contains citric acid, sodium chloride, water for injections, sodium hydroxide.
Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
200 mg/10 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Before use, dilute to 4 mg/ml.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Diluted solution: use within 12 hours and store at or below 25°C. Please refer to the leaflet.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
UK

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR THE 25 ML VIAL

1. NAME OF THE MEDICINAL PRODUCT

BRINAVESS 20 mg/ml concentrate for solution for infusion
vernakalant hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 25 ml vial contains 500 mg vernakalant hydrochloride equivalent to 452.5 mg vernakalant free base.

3. LIST OF EXCIPIENTS

Contains citric acid, sodium chloride, water for injections, sodium hydroxide.
Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
500 mg/25 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Before use, dilute to 4 mg/ml.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Diluted solution: use within 12 hours and store at or below 25°C. Please refer to the leaflet.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
UK

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for the 10 ml Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

BRINAVESS 20 mg/ml sterile concentrate
vernakalant hydrochloride
IV use

2. METHOD OF ADMINISTRATION

Dilute before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg/10 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for the 25 ml vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

BRINAVESS 20 mg/ml sterile concentrate
vernakalant hydrochloride
IV use

2. METHOD OF ADMINISTRATION

Dilute before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 mg/25 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

BRINAVESS 20 mg/ml concentrate for solution for infusion
vernakalant hydrochloride

Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

The full name of your medicine is BRINAVESS 20 mg/ml concentrate for solution for infusion. In this leaflet the shorter name BRINAVESS is used.

In this leaflet:

1. WHAT BRINAVESS IS AND WHAT IT IS USED FOR

BRINAVESS contains the active substance vernakalant hydrochloride. BRINAVESS works by changing your irregular or fast heart beat to a normal heart beat.

In adults it is used if you have a fast, irregular heart beat called atrial fibrillation which has started recently (≤ 7 days) for non-surgery patients and ≤ 3 days for post-cardiac surgery patients. Your doctor will decide whether you should be treated with BRINAVESS.

2. BEFORE YOU ARE GIVEN BRINAVESS

You should not be given BRINAVESS if:
- you are allergic (hypersensitive) to vernakalant hydrochloride or any of the other ingredients of BRINAVESS (see section 6)
- you have had new or worsening chest pain (angina) diagnosed by your doctor as an acute coronary syndrome in the last 30 days or you have had a heart attack in the last 30 days
- you have a very narrow heart valve, systolic blood pressure <100 mm Hg or advanced heart failure with symptoms at minimal exertion or at rest
- you have an abnormally slow heart rate or skipped heart beats and do not have a pacemaker, or you have conduction disturbance called QT prolongation - which can be seen on an ECG by your doctor
- you have been given certain other intravenous medicines (anti-arrhythmics Class I and III) used to normalize an abnormal heart rhythm, 4 hours before BRINAVESS is to be given

You should not be given BRINAVESS if any of the above apply to you. If you are not sure, talk to your doctor before you are given this medicine.

Take special care with BRINAVESS
Check with your doctor before you are given BRINAVESS if:
- you have any of the following problems:
  - heart failure
  - certain heart diseases involving the heart muscle, lining that surrounds the heart and a severe narrowing of the heart valves

- a disease of the heart valves
- liver problems
- you are taking other rhythm control medicines

If you have very low blood pressure or slow heart rate or certain changes in your ECG while using this medicine, your doctor may stop your treatment.
Your doctor will consider if you need additional rhythm control medicine 4 hours after BRINAVESS.
BRINAVESS may not work in treating some other kinds of abnormal heart rhythms, however your doctor will be familiar with these
Tell your doctor if you have a pacemaker.

If any of the above apply to you (or you are not sure), talk to your doctor.

Blood tests
Before giving you this medicine, your doctor will decide whether to test your blood to see how well it clots and also to see your potassium level.

Use in Children
There is no experience on the use of BRINAVESS in children and adolescents less than 18 years of age; therefore its use is not recommended.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or herbal medicines and natural products.

Pregnancy and breast-feeding
- Talk to your doctor before having this medicine if you are pregnant or might become pregnant. This is because it is preferable to avoid the use of BRINAVESS during pregnancy.
- If you are breast-feeding or planning to breast-feed you should talk to your doctor before you are given BRINAVESS. This is because it should be used with care as it is not known whether BRINAVESS passes into the breast milk.

Ask your doctor for advice before taking any medicine, if you are pregnant or breast-feeding.

Driving and using machines
It should be taken into account that some people may get dizzy after receiving BRINAVESS, usually within the first two hours. (See POSSIBLE SIDE EFFECTS.) If you get dizzy, you should avoid driving or operating machinery after receiving BRINAVESS.

Important information about some of the ingredients of BRINAVESS
This medicinal product contains approximately 1.4 mmol (32 mg) sodium in each 200 mg vial.
Each vial of 500 mg contains approximately 3.5 mmol (80 mg) of sodium.
Take into consideration if you are on a controlled sodium diet.

3. HOW BRINAVESS IS GIVEN

- BRINAVESS will be given to you by a health care professional.
- It will be given to you into your vein over 10 minutes.
- The amount of BRINAVESS you may be given will depend on your weight. The recommended initial dose is 3 mg/kg. While you are being given BRINAVESS, your breathing, heart beat, blood pressure and the electrical activity of your heart will be checked.
- If your heart beat has not returned to normal 15 minutes after the end of your first dose, you may be given a second dose. This will be a slightly lower dose of 2 mg/kg. Total doses of greater than 5 mg/kg should not be administered within 24 hours.

If you are given more BRINAVESS than you should

If you think that you may have been given too much BRINAVESS, tell your doctor straight away.

If you have any further questions on the use of this medicine, ask your doctor.

4. POSSIBLE SIDE EFFECTS

The following terms are used to describe how often side effects have been reported.
very common: affects more than 1 user in 10
common: affects 1 to 10 users in 100
uncommon: affects 1 to 10 users in 1,000

Like all medicines, BRINAVESS can cause side effects, although not everybody gets them.
Your doctor may decide to stop the infusion if your doctor observes any abnormal changes of:
- your heart beat
- your blood pressure
- the electrical activity of your heart

Very common side effects seen within 24 hours of being given BRINAVESS include:
- taste disturbances
- sneezing

These effects should pass quickly.

Other side effects include:
Common:
- numbness or pain at the infusion site, numbness or decreased skin sensation, tingling feelings or numbness
- nausea and vomiting
- feeling hot and tired
- low blood pressure, slow, fast or irregular heart beat,feeling dizzy
- headache
- coughing,dry mouth,sore nose
- sweating,itching

Uncommon:
- certain kinds of heart beat problems, (such as a short pause in the normal activity of your heart or a missed beat;awareness of your heart beating (palpitations))
- eye irritation or watery eyes or changes in your vision;a change in your sense of smell;pain in your fingers and toes; a burning feeling; cold sweats; hot flush; itching
- urgency to have a bowel movement; diarrhoea
- shortness of breath or a tight chest
- irritation at the infusion site
- feeling light-headed or fainting;generally feeling unwell;feeling drowsy or sleepy
- runny nose; sore throat
- pale skin

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE BRINAVESS

Keep out of the reach and sight of children.

Do not use BRINAVESS after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

BRINAVESS must be diluted before it is used. The diluted sterile concentrate is chemically and physically stable for 12 hours at or below 25° C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2° C to 8 C, unless dilution has taken place in controlled and validated aseptic conditions.

Do not administer BRINAVESS if you notice particulate matter or discolouration.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What BRINAVESS contains

- The active substance is vernakalant hydrochloride. Each ml of concentrate contains 20 mg vernakalant hydrochloride equivalent to 18.1 mg vernakalant free base.
  Each vial of 200 mg vernakalant hydrochloride is equivalent to 181 mg vernakalant free base.
  Each vial of 500 mg of vernakalant hydrochloride is equivalent to 452.5 mg of vernakalant free base.
- The other ingredients are citric acid, sodium chloride, sodium hydroxide and water for injection.

What BRINAVESS looks like and contents of the pack

BRINAVESS is a concentrate for solution for infusion (sterile concentrate) which is clear and colourless to pale yellow.

Pack size of 1 vial

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Manufacturer:

Merck Sharp & Dohme B. V.
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NL-2003 PC Haarlem
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in {MM/YYYY}**.**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for medical or healthcare professionals only:

Please refer to the Summary of Product Characteristics and the educational material for additional information prior to the use of BRINAVESS

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults
-For non-surgery patients: atrial fibrillation ≤ 7 days duration
-For post-cardiac surgery patients: atrial fibrillation ≤ 3 days duration

4.2 Posology and method of administration

BRINAVESS should be administered by intravenous infusion, by qualified medical personnel in a monitored clinical setting appropriate for cardioversion.

Posology
BRINAVESS is dosed by patient body weight, with a maximum calculated dose based upon 113 kgs. The recommended initial infusion is 3 mg/kg to be infused over a 10 minute period. For patients weighing ≥ 113 kg, do not exceed the maximum initial dose of 339 mg (84.7 ml of 4 mg/ml solution). If conversion to sinus rhythm does not occur within 15 minutes after the end of the initial infusion, a second 10 minute infusion of 2 mg/kg may be administered. For patients weighing ≥ 113 kg, do not exceed the maximum second infusion of 226 mg (56.5 ml of 4 mg/ml solution) .Cumulative doses of greater than 5 mg/kg should not be administered within 24 hours. There are no clinical data on repeat doses after the initial and second infusions. By 24 hours there appears to be insignificant levels of vernakalant.

If conversion to sinus rhythm occurs during either the initial or second infusion, that infusion should be continued to completion. If haemodynamically stable atrial flutter is observed after the initial infusion, the second infusion of BRINAVESS may be administered as patients may convert to sinus rhythm. (See sections 4.4 and 4.8.)

An infusion pump is the preferred delivery device. However, a syringe pump is acceptable provided that the calculated volume can be accurately given within the specified infusion time.

Do not administer as an intravenous push or bolus.

Recommended diluents are 0.9% Sodium Chloride for Injection, Lactated Ringers for Injection, or 5% Glucose for Injection.

Read all steps before administration.

Preparation of BRINAVESS for infusion

Step 1: Visually inspect BRINAVESS vials for particulate matter and discolouration before administration. Do not use any vials exhibiting particulate matter or discolouration. Note: BRINAVESS concentrate for solution for infusion ranges from colourless to pale yellow. Variations of colour within this range do not affect potency.

Step 2: Dilution of concentrate
To ensure proper administration, a sufficient amount of BRINAVESS 20 mg/ml should be prepared at the outset of therapy to deliver the initial and second infusion should it be warranted.
Create a solution with a concentration of 4 mg/ml following the dilution guidelines below:
Patients ≤ 100 kg: 25 ml of BRINAVESS 20 mg/ml is added to 100 ml of diluent.
Patients > 100 kg: 30 ml of BRINAVESS 20 mg/ml is added to 120 ml of diluent.

Step 3: Inspect solution
The diluted sterile solution should be clear, colourless to pale yellow. Visually re-inspect the solution for particulate matter and discolouration before administering.

Method of administration
BRINAVESS vials are for single use only and must be diluted prior to administration.

Step 4: Administration of the initial infusion
The initial infusion of BRINAVESS is administered as a 3 mg/kg dose over 10 minutes.

Step 5: Patient observation
If conversion to sinus rhythm has not occurred, observe the patient's vital signs and cardiac rhythm for an additional 15 minutes.

Step 6: Administration of second infusion
If conversion to sinus rhythm did not occur with the initial infusion or within the 15 minute observation period, administer a 2 mg/kg second infusion over 10 minutes.

Cumulative doses above 565 mg have not been evaluated.

Post-cardiac surgery patients:
No dose adjustment necessary.

Renal impairment:
No dose adjustment necessary (see section 5.2).

Hepatic impairment:
No dose adjustment necessary (see sections 4.4 and 5.2).

Elderly (≥ 65 years):
No dose adjustment necessary.

*Paediatric population**:***
There is no relevant use of BRINAVESS in children and adolescents < 18 years of age in the current indication and therefore should not be used in this population.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see section 6.1).
- Patients with severe aortic stenosis, patients with systolic blood pressure < 100 mm Hg, and patients with heart failure class NYHA III and NYHA IV.
- Patients with prolonged QT at baseline (uncorrected > 440 msec), or severe bradycardia, sinus node dysfunction or second degree and third degree heart block in the absence of a pacemaker.
- Use of intravenous rhythm control anti-arrhythmics (class I and class III) within 4 hours prior to BRINAVESS administration.

- Acute coronary syndrome (including myocardial infarction) within the last 30 days.

4.4 Special warnings and precautions for use

Patients should be observed with assessment of vital signs and continuous cardiac rhythm monitoring during and after administration of BRINAVESS, until clinical and ECG parameters have stabilised.

Direct-current cardioversion may be considered for patients who do not respond to therapy. There is no clinical experience with direct-current cardioversion under two hours postdose.

Prior to attempting pharmacological cardioversion, ensure that patients are adequately hydrated and haemodynamically optimized and if necessary patients should be anticoagulated in accordance with treatment guidelines. In patients with uncorrected hypokalemia (serum potassium of less than 3.5 mmol/l), potassium levels should be corrected prior to use of BRINAVESS.

During infusion of BRINAVESS, if patients develop clinically meaningful bradycardia and/or hypotension or develop ECG changes (such as a clinically meaningful sinus pause, complete heart block, new bundle branch block, significant prolongation of the QRS or QT interval, changes consistent with ischaemia or infarction and ventricular arrhythmia), the administration of BRINAVESS should be discontinued and these patients should receive appropriate medical management. If these events occur during the first infusion of BRINAVESS, patients should not receive the second dose of BRINAVESS.

Hypotension
Hypotension can occur in a small number of patients (vernakalant 7.6 %, placebo 5.1%). Hypotension typically occurs early, either during the infusion or early after the end of the infusion, and can usually be corrected by standard supportive measures. Patients with congestive heart failure (CHF) have been identified as a population at higher risk for hypotension. (See section 4.8.)

Congestive Heart Failure
Patients with CHF showed a higher overall incidence of hypotensive events, during the first 2 hours after dose in patients treated with vernakalant compared to patients receiving placebo (16.1% versus 4.7%, respectively). In patients without CHF the incidence of hypotension was not significantly different during the first 2 hours after dose in patients treated with vernakalant compared to patients receiving placebo (5.7% versus. 5.2%, respectively). Hypotension reported as a serious adverse experience or leading to medicine discontinuation occurred in CHF patients following exposure to BRINAVESS in 2.9% of these patients compared to 0% in placebo.

Patients with a history of CHF showed a higher incidence of ventricular arrhythmia in the first two hours post dose (7.3% for BRINAVESS compared to 1.6% in placebo). These arrhythmias typically presented as asymptomatic, monomorphic, non-sustained (average 3-4 beats) ventricular tachycardias. By contrast, ventricular arrhythmias were reported with similar frequencies in patients without a history of CHF who were treated with either BRINAVESS or placebo (3.2% for BRINAVESS versus 3.6% for placebo).

Due to the higher incidence of the adverse events of hypotension and ventricular arrhythmia in patients with CHF, vernakalant should be used cautiously in haemodynamically stable patients with CHF functional classes NYHA I to II. There is limited experience with the use of vernakalant in patients with previously documented LVEF $\leq$ 35%, its use in these patients is not recommended. The use in CHF patients corresponding to NYHA III or NYHA IV is contraindicated (see section 4.3).

Atrial Flutter
BRINAVESS was not found to be effective in converting typical primary atrial flutter to sinus rhythm. Patients receiving BRINAVESS have a higher incidence of converting to atrial flutter within the first 2 hours post-dose. This risk is higher in patients who use Class I antiarrhythmics (see section 4.8). If atrial flutter is observed as secondary to treatment, continuation of infusion should be considered (see section 4.2)

Use of AADs (anti-arrhythmic drugs) prior to or after BRINAVESS
BRINAVESS can not be recommended in patients previously administered intravenous AADs (class I and III) 4-24 hours prior to vernakalant, due to lack of data. BRINAVESS should not be administered in patients who received intravenous AADs (class I and III) within 4 hours prior to vernakalant (see section 4.3).

BRINAVESS should be used with caution in patients on oral AADs (class I and III), due to limited experience. Risk of atrial flutter may be increased in patients receiving class I AADs (see above).

There is limited experience with the use of intravenous rhythm control anti-arrhythmics (class I and class III) in the first 4 hours after BRINAVESS administration, therefore these agents should be used cautiously within this period. Resumption or initiation of oral maintenance antiarrhythmic therapy can be considered starting 2 hours after vernakalant administration.

Valvular Heart Disease
In patients with valvular heart disease, there was a higher incidence of ventricular arrhythmia events in vernakalant patients. These patients should be monitored closely.

Other Diseases and Conditions not Studied
BRINAVESS has been administered to patients with an uncorrected QT less than 440 msec without an increased risk of torsade de pointes.

Furthermore, BRINAVESS has not been evaluated in patients with clinically meaningful valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis and its use can not be recommended in such cases. There is limited experience with BRINAVESS in patients with pacemakers.

As the clinical trial experience in patients with advanced hepatic impairment is limited, vernakalant is not recommended in these patients.

This medicinal product contains approximately 1.4 mmol (32 mg) sodium in each 200 mg vial. Each vial of 500 mg contains approximately 3.5 mmol (80 mg) of sodium. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been undertaken with vernakalant injection. Within the clinical development program, oral maintenance antiarrhythmic therapy was halted for a minimum of 2 hours after BRINAVESS administration. Resumption or initiation of oral maintenance antiarrhythmic therapy after this time period can be considered (see sections 4.3 and 4.4).

Although vernakalant is a substrate of CYP2D6, population pharmacokinetic (PK) analyses demonstrated that no substantial differences in the acute exposure of vernakalant (Cmax and AUC0-90 min) were observed when weak or potent CYP2D6 inhibitors were administered within 1 day prior to vernakalant infusion compared to patients that were not on concomitant therapy with CYP2D6 inhibitors. In addition, acute exposure of vernakalant in poor metabolisers of CYP2D6 is only minimally different when compared to that of extensive metabolisers. No dose adjustment of vernakalant is required on the basis of CYP2D6 metaboliser status, or when vernakalant is administered concurrently with 2D6 inhibitors.

Vernakalant is a moderate, competitive inhibitor of CYP2D6 However, acute intravenous administration of vernakalant is not expected to markedly impact the PK of chronically administered 2D6 substrates, as a consequence of vernakalant's short half life and the ensuing transient nature of 2D6 inhibition. Vernakalant given by infusion is not expected to perpetrate meaningful drug drug interactions due to the rapid distribution and transient exposure, low protein binding, lack of inhibition

of other CYP P450 enzymes tested (CYP3A4, 1A2, 2C9, 2C19 or 2E1) and lack of P-glycoprotein inhibition in a digoxin transport assay.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements BRINAVESS does not contain a preservative.