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.

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

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

Excipient with known effect

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) sodium.

Each ml 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 (5 % glucose solution for injection) or 3.2 mg sodium (Lactated Ringers solution for injection).

For the 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

Brinavess is indicated in adults for rapid conversion of recent onset atrial fibrillation to sinus rhythm
-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

Vernakalant should be administered in a monitored clinical setting appropriate for cardioversion. Only a well-qualified healthcare professional should administer it.

Posology

Vernakalant is dosed by patient body weight, with a maximum calculated dose based upon 113 kg. The recommended initial infusion is 3 mg/kg to be infused over a 10-minute period with a 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 (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.

The initial infusion is administered as a 3 mg/kg dose over 10 minutes. During this period, the patient should be carefully monitored for any signs or symptoms of a sudden decrease in blood pressure or heart rate. If such signs develop, with or without symptomatic hypotension or bradycardia, the infusion should be stopped immediately.

If conversion to sinus rhythm has not occurred, the patient's vital signs and cardiac rhythm should be observed for an additional 15 minutes.

If conversion to sinus rhythm did not occur with the initial infusion or within the 15-minute observation period, a 2 mg/kg second infusion should be administered over 10 minutes.

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 may be administered as patients may convert to sinus rhythm (see sections 4.4 and 4.8).

Patients with body weight > 113 kg
For patients above 113 kg, vernakalant has a fixed dose. The initial dose is 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 226 mg (56.5 ml of 4 mg/ml solution) may be administered. Cumulative doses above 565 mg have not been evaluated.

Post-cardiac surgery
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 vernakalant in children and adolescents < 18 years of age for rapid conversion of recent onset atrial fibrillation to sinus rhythm and therefore it should not be used in this population.

Method of administration

For intravenous use.

Vernakalant should not be administered as an intravenous push or bolus.

The vials are for single use only and must be diluted prior to administration.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in 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 ms), 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 antiarrhythmics (class I and class III) within 4 hours prior to, as well as in the first 4 hours after, vernakalant administration.
- Acute coronary syndrome (including myocardial infarction) within the last 30 days.

4.4 Special warnings and precautions for use

Patient monitoring

Cases of serious hypotension have been reported during and immediately following vernakalant infusion. Patients should be carefully observed for the entire duration of the infusion and for at least 15 minutes after completion of the infusion with assessment of vital signs and continuous cardiac rhythm monitoring.

If any of the following signs or symptoms occurs, the administration of vernakalant should be discontinued and these patients should receive appropriate medical management:
- A sudden drop in blood pressure or heart rate, with or without symptomatic hypotension or bradycardia
- Hypotension
- Bradycardia
- 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)

If these events occur during the first infusion of vernakalant, patients should not receive the second dose.

The patient should be further monitored for 2 hrs after the start of infusion and until clinical and ECG parameters have stabilised.

Precautions before infusion

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

A pre-infusion checklist is provided with the medicinal product. Prior to administration the prescriber is asked to determine eligibility of the patient through use of the supplied checklist. The checklist should be placed on the infusion container to be read by the healthcare professional who will administer it.

Hypotension

Hypotension can occur in a small number of patients (vernakalant 5.7 %, placebo 5.5 % in the first 2 hours post-dose). 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. Uncommonly, cases of severe hypotension have been observed. Patients with congestive heart failure (CHF) have been identified as a population at higher risk for hypotension (see section 4.8).

The patient is required to be monitored for signs and symptoms of a sudden decrease in blood pressure or heart rate for the duration of the infusion and for at least 15 minutes after the completion of the infusion.

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 (13.4 % *versus* 4.7 %, respectively). Hypotension reported as a serious adverse experience or leading to medicinal product discontinuation occurred in CHF patients following exposure to vernakalant in 1.8 % of these patients compared to 0.3 % in placebo.

Patients with a history of CHF showed a higher incidence of ventricular arrhythmia in the first two hours post dose (6.4% for vernakalant compared to 1.6% in placebo). These arrhythmias typically presented as asymptomatic, monomorphic, non-sustained (average 3-4 beats) ventricular tachycardias.

Due to the higher incidence of the adverse reactions 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).

Valvular heart disease

In patients with valvular heart disease, there was a higher incidence of ventricular arrhythmia events in vernakalant patients until 24 hours after dosing. Within the first 2 hours, ventricular arrhythmia occurred in 6.4 % of patients treated with vernakalant versus none after placebo. These patients should be monitored closely.

Atrial flutter

Vernakalant was not found to be effective in converting typical primary atrial flutter to sinus rhythm. Patients receiving vernakalant 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). In post-marketing experience rare cases of atrial flutter with 1:1 atrioventricular conduction are observed.

Other diseases and conditions not studied

Vernakalant has been administered to patients with an uncorrected QT less than 440 ms without an increased risk of torsade de pointes.

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

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

There are no clinical data on repeat doses after the initial and second infusions.

Electrical cardioversion

Direct-current cardioversion may be considered for patients who do not respond to therapy. There is no clinical experience with direct-current cardioversion under 2 hours post-dose.

Use of AADs (antiarrhythmic drugs) prior to or after vernakalant

Vernakalant cannot be recommended in patients previously administered intravenous AADs (class I and III) 4-24 hours prior to vernakalant due to lack of data. It must not be administered in patients who received intravenous AADs (class I and III) within 4 hours prior to vernakalant (see section 4.3).

Vernakalant 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 antiarrhythmics (class I and class III) in the first 4 hours after vernakalant administration, therefore these agents must not be used within this period (see section 4.3).

Resumption or initiation of oral maintenance antiarrhythmic therapy can be considered starting 2 hours after vernakalant administration.

Sodium content

This medicinal product contains 32 mg sodium per 200 mg vial, equivalent to 1.6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This medicinal product contains 80 mg sodium per 500 mg vial, equivalent to 4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Vernakalant must not be administered in patients who received intravenous AADs (class I and III) within 4 hours prior to vernakalant (see section 4.3).

Within the clinical development program, oral maintenance antiarrhythmic therapy was halted for a minimum of 2 hours after vernakalant 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 (C_{max} and $AUC_{0\text{-}90min}$) 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. Studies in animal 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 newborns/infants cannot be excluded.
Caution should be exercised when used in breast-feeding women.

Fertility

Vernakalant was not shown to alter fertility in animal studies.

4.7 Effects on ability to drive and use machines

Vernakalant has minor to moderate influence on the ability to drive and use machines. Dizziness has been reported within the first 2 hours after receiving it (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions (> 5 %) seen in the first 24 hours after receiving vernakalant were dysgeusia (taste disturbance) (17.9 %), sneezing (12.5 %), and paraesthesia (6.9 %). These reactions occurred around the time of infusion, were transient and were rarely treatment limiting.

Tabulated list of adverse reactions

The adverse reaction profile presented below is based on the analysis of pooled clinical trials, a post-authorisation safety study and spontaneous reporting. 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).

Table 1: Adverse reactions [a]

Nervous system disorders	*Very common:* Dysgeusia *Common:* Paraesthesia; dizziness *Uncommon:* Hypoaesthesia; burning sensation; parosmia; syncope; somnolence
Eye disorders	*Uncommon:* Lacrimation increased; eye irritation; visual impairment
Cardiac disorders	*Common:* Bradycardia [b]; atrial flutter [b] *Uncommon*: Sinus arrest; ventricular tachycardia; palpitations; bundle branch block left; ventricular extrasystoles; AV block first degree; AV block complete; bundle branch block right; sinus bradycardia; ECG QRS complex prolonged; cardiogenic shock, blood pressure diastolic increased *Rare:* Atrial flutter with 1:1 atrioventricular conduction [b, c]
Vascular disorders	*Common:* Hypotension *Uncommon:* Flushing; hot flush; pallor

Respiratory, thoracic and mediastinal disorders	*Very common:* Sneezing *Common:* Cough; nasal discomfort *Uncommon:* Dyspnoea; throat irritation; oropharyngeal pain; nasal congestion; suffocation feeling; choking sensation; rhinorrhoea
Gastrointestinal disorders	*Common:* Nausea; paraesthesia oral; vomiting *Uncommon:* Dry mouth; diarrhoea; hypoaesthesia oral; defecation urgency
Skin and subcutaneous tissue disorders	*Common:* Pruritus; hyperhidrosis *Uncommon:* Pruritus generalised; cold sweat
Musculoskeletal and connective tissue disorders	*Uncommon:* Pain in extremity
General disorders and administration site conditions	*Common:* Infusion site pain; feeling hot; infusion site paraesthesia *Uncommon:* Fatigue; infusion site irritation; infusion site hypersensitivity; infusion site pruritus; malaise

[a] The adverse reactions included in the table occurred within 24 hours of administration of vernakalant (see sections 4.2 and 5.2) with an incidence > 0.1 % of vernakalant patients and higher than placebo
[b] See subheadings atrial flutter and bradycardia below
[c] Identified in post-marketing experience

Description of selected adverse reactions

Clinically significant adverse reactions observed in clinical trials included hypotension and ventricular arrhythmia (see section 4.4).

Bradycardia
Bradycardia was observed predominantly at the time of conversion to sinus rhythm. With a significantly higher conversion rate in patients treated with vernakalant, the incidence of bradycardia events was higher within the first 2 hours in vernakalant treated patients than in placebo-treated patients (1.6 % *versus* 0 %, respectively). Of the patients who did not convert to sinus rhythm, the incidence of bradycardia events in the first 2 hours post-dose was similar in placebo and vernakalant treated groups (4.0% and 3.8%, respectively). In general, bradycardia responded well to discontinuation of treatment and/or administration of atropine.

Atrial flutter
Atrial fibrillation patients receiving vernakalant have a higher incidence of converting to atrial flutter within the first 2 hours post-dose (1.2 % *versus* 0 % in placebo). With continuation of the 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 vernakalant did not develop 1:1 atrioventricular conduction. However, in post-marketing experience rare cases of atrial flutter with 1:1 atrioventricular conduction are observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

One patient who received 3 mg/kg of vernakalant 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 medicinal product 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 regulated by ion channels 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.

Pharmacodynamic effects

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 medicinal product toward rapidly activating and partially depolarised atrial tissue rather than toward the normally polarised 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 ms and 18.8 ms placebo-subtracted peaks after first and second infusions, respectively). By 90 minutes after the start of infusion, this difference was reduced to 8.1 ms.

Clinical efficacy and safety

Clinical Trial Design: The clinical effect of vernakalant 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 vernakalant 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 vernakalant 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 vernakalant 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 vernakalant 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 2 possible dose steps. In the performed clinical studies, the additive effect of the second dose, if any, cannot 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

Vernakalant 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 medicinal products, use of antiarrhythmic medicinal products, use of warfarin, history of ischaemic heart disease, renal impairment or expression of the cytochrome P450 2D6 enzyme.

Treatment with vernakalant 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 medicinal product 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 vernakalant 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 vernakalant effectively converted atrial

fibrillation to sinus rhythm (47.0 % vernakalant, 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).

Efficacy from Post-Marketing Observational Study
In the post-approval safety study SPECTRUM that included 1,778 patients with 2,009 BRINAVESS treatment episodes, effectiveness was assessed as the proportion of patients who converted to sinus rhythm for at least one (1) minute within 90 minutes from the start of the infusion, excluding patients who received electrical cardioversion or intravenous Class I/III antiarrhythmics for cardioversion within the 90-minute window. Overall, BRINAVESS was effective in 70.2% (1,359/1,936) of these patients. Median time to conversion to SR as reported among all patients who, as per the investigator judgement, converted to SR was 12 minutes and in most of the treatment episodes (60.4%) only one infusion was administered. The higher cardioversion rate in SPECTRUM as compared to clinical phase 3 studies (70.2% *vs* 47% to 51%) is correlated with a shorter duration of the duration of the index atrial fibrillation period (median duration of 11.1 hours in SPECTRUM *vs* 17.7 to 28.2 hours in clinical studies).

If patients who received electrical cardioversion, intravenous antiarrhythmics or oral propafenone/flecainide within 90 minutes from the start of the infusion are regarded as treatment failures in addition to patients who did not convert for one minute within 90 minutes, the conversion rate among the 2,009 patients who received BRINAVESS was 67.3 % (1,352/2,009). There was no meaningful difference when stratifying the analysis by therapeutic indication (i.e. non-surgery and post-cardiac surgery patients).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with vernakalant 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 C_{max} 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

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. By 24 hours there appears to be insignificant levels of vernakalant.

Special patient groups

Acute vernakalant pharmacokinetics is not significantly influenced by gender, history of congestive heart failure, renal impairment, or concomitant administration of beta blockers and other medicinal products, including warfarin, metoprolol, furosemide and digoxin. In patients with hepatic impairment, exposures were elevated by 9 to 25 %. No dose adjustment 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 reveal 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, embryo-foetal 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 embryo-foetal 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 embryo-foetal lethality, increased number of foetuses 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 injections
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 6.6.

6.3 Shelf life

5 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 medicinal 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 after dilution of the 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 10 ml or 25 ml of concentrate.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Read all steps before administration.

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.

Preparation of BRINAVESS for infusion

Step 1:
BRINAVESS vials should be visually inspected for particulate matter and discolouration before administration. Any vials exhibiting particulate matter or discolouration should not be used.
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.

Recommended diluents are sodium chloride 9 mg/ml (0.9 %) solution for injection, Lactated Ringers solution for injection, or 5 % glucose solution for injection.

Step 3: Inspection of the solution
The diluted sterile solution should be clear, colourless to pale yellow. The solution should be visually re-inspected for particulate matter and discolouration before administering.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Advanz Pharma Limited
Unit 17, Northwood House
Northwood Crescent
Dublin 9, D09 V504
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/10/645/001
EU/1/10/645/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 September 2010
Date of latest renewal: 02 June 2020

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Geodis CL Netherlands B.V.
Columbusweg 16
5928 LC Venlo
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder shall provide a check list in each pack, the text of which is included in Annex IIIA. The company will start to include the pre-infusion check list in packs packed at the packaging site as soon as possible but at the latest on 15 November 2012. The check list will be provided with an adhesive in order to be placed on the infusion container.

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

The Marketing Authorisation Holder must agree about the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution.

Key elements to be included in the educational material:

1. BRINAVESS should be administered by intravenous infusion in a monitored clinical setting appropriate for cardioversion. Only a well-qualified healthcare professional should administer BRINAVESS and should frequently monitor the patient for the duration of the infusion and for at least 15 minutes after the completion of the infusion for signs and symptoms of a sudden decrease in blood pressure or heart rate (see section 4.4).

2. Appropriate measures to manage and minimise 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:
  - Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
  - Patients with prolonged QT at baseline (uncorrected > 440 ms), 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 antiarrhythmics (class I and class III) within 4 hours prior to, as well as in the first 4 hours after, 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 reactions, which may occur after BRINAVESS administration, including hypotension, bradycardia, atrial flutter, or ventricular arrhythmia.
- Alert HCP for use of antiarrhythmic drugs (AADs) prior to or after BRINAVESS.
  - BRINAVESS cannot 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 not be used 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 200 mg vernakalant hydrochloride equivalent to 181 mg vernakalant.
Each vial contains 500 mg vernakalant hydrochloride equivalent to 452.5 mg vernakalant.

3. LIST OF EXCIPIENTS

Contains citric acid, sodium chloride, water for injections, sodium hydroxide (E524).

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 vial
200 mg/10 ml

1 vial
500 mg/25 ml

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after dilution.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP
Diluted solution: use within 12 hours and store at or below 25 °C.

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

Advanz Pharma Limited
Unit 17, Northwood House
Northwood Crescent
Dublin 9, D09 V504
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

10 mL:
EU/1/10/645/001

25 mL:
EU/1/10/645/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

BRINAVESS 20 mg/ml sterile concentrate
vernakalant hydrochloride
IV

2. METHOD OF ADMINISTRATION

Dilute before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mL:
200 mg/10 ml

25 mL:
500 mg/25 mL

6. OTHER

PARTICULARS TO APPEAR WITHIN THE OUTER PACKAGING (CARTON)

PRE-INFUSION CHECK-LIST

Important Instructions when using BRINAVESS

Prior to administration the prescriber is asked to determine eligibility of the patient through use of the supplied checklist. The checklist should be placed on the infusion container to be read by the healthcare professional who will administer BRINAVESS.

BRINAVESS should be administered in a monitored clinical setting appropriate for cardioversion by a well-qualified healthcare professional. Patients should be frequently monitored for the duration of the infusion and for at least 15 minutes after the completion of the infusion for signs and symptoms of a sudden decrease in blood pressure or heart rate.

Read carefully the Summary of Product Characteristics and the Health Care Professional Information Card prior to the administration of BRINAVESS

BRINAVESS must NOT be given to any patients with a "YES" response below:

Does the patient have heart failure class NYHA III or NYHA IV? **YES NO**
Has the patient presented with an acute coronary syndrome (including myocardial infarction) in the last 30 days? **YES NO**
Does the patient have severe aortic stenosis? **YES NO**
Does the patient have a systolic blood pressure < 100 mm Hg? **YES NO**
Does the patient have prolonged QT interval at baseline (uncorrected > 440 ms)? **YES NO**
Does the patient have severe bradycardia, sinus node dysfunction or second and third degree heart block, in the absence of a pacemaker? **YES NO**
Has the patient received an intravenous rhythm control antiarrhythmic drug (class I and/or class III) within 4 hours of the time when BRINAVESS will be infused? **YES NO**
Does the patient have hypersensitivity to the active substance or to any of the excipients? **YES NO**

Do NOT give other IV antiarrhythmic medicines (class I and/or class III) for at least 4 hours after infusion of BRINAVESS.

When giving BRINAVESS, follow these instructions:

- The patient should be adequately hydrated and haemodynamically optimised and adequately anticoagulated (if necessary) prior to administering BRINAVESS
- Observe the patient frequently and carefully for the entire duration of the infusion and for at least 15 minutes after completion of the infusion for:
    - Any signs or symptoms of a sudden decrease in blood pressure or heart rate, with or without symptomatic hypotension or bradycardia
    - Bradycardia
    - Hypotension
    - Unexpected ECG changes (see SmPC)

  If such signs develop, discontinue BRINAVESS immediately and provide appropriate medical management. Do not re-start BRINAVESS.

- Continue to monitor the patient for 2 hrs after the start of infusion and until clinical and ECG parameters have stabilised.

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 start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What BRINAVESS is and what it is used for
2. What you need to know before you use BRINAVESS
3. How to use BRINAVESS
4. Possible side effects
5. How to store BRINAVESS
6. Contents of the pack and other information

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, less than or equivalent to 7 days, for non-surgery patients and less than or equivalent to 3 days for post-cardiac surgery patients.

2. What you need to know before you use BRINAVESS

Do not use BRINAVESS
- if you are allergic to vernakalant hydrochloride or any of the other ingredients of this medicine (listed in section 6)
- if 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
- if you have a very narrow heart valve, systolic blood pressure less than 100 mm Hg or advanced heart failure with symptoms at minimal exertion or at rest
- if 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
- if you take certain other intravenous medicines (antiarrhythmics Class I and III) used to normalise an abnormal heart rhythm, 4 hours before BRINAVESS is to be used

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

Warnings and precautions
Talk to your doctor before using BRINAVESS if you have:
- 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 will stop your treatment.
Your doctor will consider if you need additional rhythm control medicine 4 hours after using 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. Detailed information on warnings and precautions relating to side effects that could occur are presented in section 4.

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.

Children and adolescents
Do not give this medicine to children and adolescents less than 18 years of age because there is no experience on its use in this population.

Other medicines and BRINAVESS
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Do not use BRINAVESS if you take certain other intravenous medicines (antiarrhythmics Class I and III) used to normalise an abnormal heart rhythm, 4 hours before BRINAVESS is to be used.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

It is preferable to avoid the use of BRINAVESS during pregnancy.
It is not known whether BRINAVESS passes into the breast milk.

Driving and using machines
It should be taken into account that some people may get dizzy after receiving BRINAVESS, usually within the first 2 hours (see section “Possible side effects”). If you get dizzy, you should avoid driving or operating machinery after receiving BRINAVESS.

BRINAVESS contains sodium
This medicine contains 32 mg sodium (main component of cooking/table salt) in each 200 mg vial. This is equivalent to 1.6 % of the recommended maximum daily dietary intake of sodium for an adult.
This medicine contains 80 mg of sodium (main component of cooking/table salt) in each vial of 500 mg. This is equivalent to 4 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use BRINAVESS

The amount of BRINAVESS you may be given will depend on your weight. The recommended initial dose is 3 mg/kg, with a maximum calculated dose based upon 113 kg. If you weigh more than 113 kg, you will receive a fixed dose of 339 mg. 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, with a maximum calculated dose based upon 113 kg. If you weigh more than 113 kg, you will receive a fixed dose of 226 mg. Total doses of greater than 5 mg/kg should not be administered within 24 hours.

BRINAVESS will be given to you by a health care professional. BRINAVESS will be diluted before being given to you. Information on how to prepare the solution is available at the end of this leaflet.

It will be given to you into your vein over 10 minutes.

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

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor may decide to stop the infusion if he observes any of the following abnormal changes of:
- your heart beat (such as a very fast (uncommon) or very slow heart beat (common), a missed beat (uncommon), or a short pause in the normal activity of your heart (uncommon))
- your blood pressure (such as a very low blood pressure causing a serious heart condition) (uncommon)
- the electrical activity of your heart (uncommon)

Other side effects:

Very common (may affect more than 1 in 10 people)
- taste disturbances
- sneezing

Common (may affect up to 1 in 10 people)
- fast heart beat
- pain or numbness at the infusion site, numbness, decreased skin sensation, or tingling feelings
- nausea and vomiting
- feeling hot
- low blood pressure, slow heart beat, feeling dizzy
- coughing, sore nose
- excessive sweating, itching
- numbness or tingling that occurs in the mucosa or tissues of the oral cavity

Uncommon (may affect up to 1 in 100 people)
- certain kinds of heart beat problems, (such as an awareness of your heart beating (palpitations) or an extra heart beat)
- decreased feeling or sensitivity
- eye irritation, 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
- urgency to have a bowel movement, diarrhoea
- shortness of breath or a tightness in the chest
- choking sensation
- pain in your mouth or throat

- irritation, itching at the infusion site
- high blood pressure
- feeling light-headed or fainting, generally feeling unwell, feeling drowsy or sleepy
- runny nose, sore throat
- stuffy nose
- dry mouth
- pale skin
- generalised itching
- fatigue
- decreased feeling or sensitivity of the mouth

These effects, seen within 24 hours of being given BRINAVESS, should pass quickly, however, if they do not you should consult your doctor.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store BRINAVESS

Keep this medicine out of the sight and reach of children.

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

This medicine 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 medicine 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 use this medicine if you notice particulate matter or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other 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.
  Each vial of 200 mg vernakalant hydrochloride is equivalent to 181 mg vernakalant.
  Each vial of 500 mg of vernakalant hydrochloride is equivalent to 452.5 mg of vernakalant.
- The other ingredients are citric acid, sodium chloride, sodium hydroxide (E524) and water for injections (see section 2 “BRINAVESS contains sodium”).

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.

BRINAVESS is available in pack of 1 vial containing 200 mg or 500 mg of vernakalant hydrochloride.

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Dublin 9, D09 V504
Ireland

Manufacturer:
Geodis CL Netherlands B.V.
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in

Other sources of information
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 healthcare professionals only:

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

CLINICAL PARTICULARS

Therapeutic indications

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

Posology and method of administration

Vernakalant should be administered in a monitored clinical setting appropriate for cardioversion. Only a well-qualified healthcare professional should administer it.

Posology

Vernakalant is dosed by patient body weight, with a maximum calculated dose based upon 113 kg. The recommended initial infusion is 3 mg/kg to be infused over a 10-minute period with a 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 (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.

The initial infusion is administered as a 3 mg/kg dose over 10 minutes. During this period, the patient should be carefully monitored for any signs or symptoms of a sudden decrease in blood pressure or heart rate. If such signs develop, with or without symptomatic hypotension or bradycardia, the infusion should be stopped immediately.

If conversion to sinus rhythm has not occurred, the patient's vital signs and cardiac rhythm should be observed for an additional 15 minutes.

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.

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 may be administered as patients may convert to sinus rhythm (see "Special warnings and precautions for use" and "Undesirable effects").

Patients with body weight > 113 kg
For patients above 113 kg, vernakalant has a fixed dose. The initial dose is 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 226 mg (56.5 ml of 4 mg/ml solution) may be administered. Cumulative doses above 565 mg have not been evaluated.

Post-cardiac surgery
No dose adjustment necessary.

Renal impairment
No dose adjustment necessary (see "Pharmacokinetic properties").

Hepatic impairment
No dose adjustment necessary (see "Special warnings and precautions for use" and "Pharmacokinetic properties").

Elderly (≥ 65 years)
No dose adjustment necessary.

Paediatric population
There is no relevant use of vernakalant in children and adolescents < 18 years of age for rapid conversion of recent onset atrial fibrillation to sinus rhythm and therefore it should not be used in this population.

Method of administration

For intravenous use.

Vernakalant should not be administered as an intravenous push or bolus.

The vials are for single use only and must be diluted prior to administration.

For instructions on dilution of the medicinal product before administration, see section "Special precautions for disposal and other handling".

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in "List of excipients".
- 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 ms), 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 antiarrhythmics (class I and class III) within 4 hours prior to, as well as in the first 4 hours after, vernakalant administration.
- Acute coronary syndrome (including myocardial infarction) within the last 30 days.

Special warnings and precautions for use

Patient monitoring

Cases of serious hypotension have been reported during and immediately following vernakalant infusion. Patients should be carefully observed for the entire duration of the infusion and for at least 15 minutes after completion of the infusion with assessment of vital signs and continuous cardiac rhythm monitoring.

If any of the following signs or symptoms occurs, the administration of vernakalant should be discontinued and these patients should receive appropriate medical management:
- A sudden drop in blood pressure or heart rate, with or without symptomatic hypotension or bradycardia
- Hypotension
- Bradycardia
- 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)

If these events occur during the first infusion of vernakalant, patients should not receive the second dose.

The patient should be further monitored for 2 hrs after the start of infusion and until clinical and ECG parameters have stabilised.

Precautions before infusion

Prior to attempting pharmacological cardioversion, patients should be adequately hydrated and haemodynamically optimised and if necessary patients should be anticoagulated in accordance with

treatment guidelines. In patients with uncorrected hypokalaemia (serum potassium of less than 3.5 mmol/l), potassium levels should be corrected prior to use of vernakalant.
A pre-infusion checklist is provided with the medicinal product. Prior to administration the prescriber is asked to determine eligibility of the patient through use of the supplied checklist. The checklist should be placed on the infusion container to be read by the healthcare professional who will administer it.

Hypotension

Hypotension can occur in a small number of patients (vernakalant 5.7 %, placebo 5.5 % in the first 2 hours post-dose). 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. Uncommonly, cases of severe hypotension have been observed. Patients with congestive heart failure (CHF) have been identified as a population at higher risk for hypotension. (see "Undesirable effects".)

The patient is required to be monitored for signs and symptoms of a sudden decrease in blood pressure or heart rate for the duration of the infusion and for at least 15 minutes after the completion of the infusion.

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 (13.4 % *versus* 4.7 %, respectively). Hypotension reported as a serious adverse experience or leading to medicinal product discontinuation occurred in CHF patients following exposure to vernakalant in 1.8 % of these patients compared to 0.3 % in placebo.

Patients with a history of CHF showed a higher incidence of ventricular arrhythmia in the first two hours post dose (6.4% for vernakalant compared to 1.6% in placebo). These arrhythmias typically presented as asymptomatic, monomorphic, non-sustained (average 3-4 beats) ventricular tachycardias. Due to the higher incidence of the adverse reactions 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 ≤ 35 %, its use in these patients is not recommended. The use in CHF patients corresponding to NYHA III or NYHA IV is contraindicated (see "Contraindications").

Valvular heart disease

In patients with valvular heart disease, there was a higher incidence of ventricular arrhythmia events in vernakalant patients until 24 hours after dosing. Within the first 2 hours, ventricular arrhythmia occurred in 6.4% of patients treated with vernakalant versus none after placebo. These patients should be monitored closely.

Atrial flutter

Vernakalant was not found to be effective in converting typical primary atrial flutter to sinus rhythm. Patients receiving vernakalant 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 "Undesirable effects"). If atrial flutter is observed as secondary to treatment, continuation of infusion should be considered (see "Posology and method of administration"). In post-marketing experience rare cases of atrial flutter with 1:1 atrioventricular conduction are observed.

Other diseases and conditions not studied

Vernakalant has been administered to patients with an uncorrected QT less than 440 ms without an increased risk of torsade de pointes.

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

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

There are no clinical data on repeat doses after the initial and second infusions.

Electrical cardioversion

Direct-current cardioversion may be considered for patients who do not respond to therapy. There is no clinical experience with direct-current cardioversion under 2 hours post-dose.

Use of AADs (antiarrhythmic drugs) prior to or after vernakalant

Vernakalant cannot be recommended in patients previously administered intravenous AADs (class I and III) 4-24 hours prior to vernakalant, due to lack of data. It must not be administered in patients who received intravenous AADs (class I and III) within 4 hours prior to vernakalant (see "Contraindications").

Vernakalant 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 antiarrhythmics (class I and class III) in the first 4 hours after vernakalant administration, therefore these agents must not be used within this period (see "Contraindications").

Resumption or initiation of oral maintenance antiarrhythmic therapy can be considered starting 2 hours after vernakalant administration.

Sodium content

This medicinal product contains 32 mg sodium per 200 mg vial, equivalent to 1.6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This medicinal product contains 80 mg sodium per 500 mg vial, equivalent to 4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Vernakalant must not be administered in patients who received intravenous AADs (class I and III) within 4 hours prior to vernakalant (see "Contraindications").

Within the clinical development program, oral maintenance antiarrhythmic therapy was halted for a minimum of 2 hours after vernakalant administration. Resumption or initiation of oral maintenance antiarrhythmic therapy after this time period can be considered (see "Contraindications" and "Special warnings and precautions for use").

Although vernakalant is a substrate of CYP2D6, population pharmacokinetic (PK) analyses demonstrated that no substantial differences in the acute exposure of vernakalant (C_{max} and $AUC_{0\text{-}90\ min}$) 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.

Special precautions for disposal and other handling

Read all steps before administration.

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.

Preparation of BRINAVESS for infusion

Step 1:
BRINAVESS vials should be visually inspected for particulate matter and discolouration before administration. Any vials exhibiting particulate matter or discolouration should not be used. 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.

Recommended diluents are sodium chloride 9 mg/ml (0.9 %) solution for injection, Lactated Ringers solution for injection, or 5 % glucose solution for injection.

Step 3: Inspection of the solution
The diluted sterile solution should be clear, colourless to pale yellow. The solution should be visually re-inspected for particulate matter and discolouration before administering.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.