BRINAVESS® 20 mg/ml

Prescribing information

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 is equivalent to 181 mg of vernakalant.
Each 25 ml vial contains 500 mg of vernakalant hydrochloride is 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) of 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

Rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults who are hemodynamically stable
-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 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).

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
Vernakalant is not indicated for children and adolescents < 18 years of age.

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 optimized 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 .

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 ≤ 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. 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 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 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 breastfeeding 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

Table 1: Adverse reactions [a]

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 administrative site conditions	*Common:* Infusion site pain, feeling hot, infusion site paraesthesia *Uncommon: F*atigue, 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 section 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 sections 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 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 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. However, in post-marketing experience very 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/
In addition, you may report by sending an e-mail message to safety@tzamal-medical.co.il

4.9 Overdose

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 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 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 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, 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

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 medicinal product, use of antiarrhythmic medicinal product, 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 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 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).

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 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 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 pharmacokineticsis 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 monohydrate (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 4.2.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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 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 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. MANUFACTURER

Correvio International Sarl, Geneva, Switzerland

8. REGISTRATION HOLDER

Tzamal Bio-Pharma Ltd, 20 Hamagshimim st., Petah-Tikva 4934829

9. DRUG REGISTRATION NUMBER

148 28 33391 00

Revised in December 2020.