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

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 Yellow Card Scheme Website: www.mhra.gov.uk/ yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store 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.

Marketing Authorisation Holder:
Mercury Pharmaceuticals Limited,
Dashwood House, 69 Old Broad Street,
London, EC2M 1QS,
United Kingdom

Manufacturer:
Geodis Logistics Netherlands B.V.
Columbusweg 16
5928 LC Venlo
The Netherlands

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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.