Government of JERSEY

Health and Community Services

Vernakalant (Brinavess®) Infusion Policy

October 2019

DOCUMENT PROFILE

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1. INTRODUCTION

1.1 Rationale

Atrial fibrillation (AF) is the most common arrhythmia and prevalence increases with age (1). However, more recent figures suggest there is now a 1 in 4 lifetime risk of developing the arrhythmia over the age of 40 years (2). Epidemiological data suggests that more than 6 million people in Europe may currently have the arrhythmia and the projected number of people with AF is set to at least double in the next 40 years (3,4,5).

Management of AF follows either a rate or rhythm control approach. When rhythm control is the preferred option, this may be through electrical cardioversion, pharmacological cardioversion using antiarrhythmic drugs or ablation. Until recently, the choice of antiarrhythmic drugs for pharmacological cardioversion was limited and some e.g. flecainide can only be given to highly selected patients. Vernakalant is a new addition to intravenous antiarrhythmic drugs available for cardioversion of AF (6).

Vernakalant is the first atrial-specific antiarrhythmic drug developed for pharmacological cardioversion of recent onset AF (7). Vernakalant has been shown to be more effective than placebo and amiodarone. The main advantage is rapid conversion of AF, which potentially reduces atrial remodelling. It can be used (unlike flecainide) in patients with little or no underlying cardiovascular disease and in patients with moderate disease such as stable coronary and hypertensive heart disease.

Vernakalant is only currently available in the intravenous form and must be given in an environment where continuous cardiac monitoring is available. Electrical cardioversion and defibrillation equipment must be easily accessible and close monitoring of vital signs is essential.

Vernakalant has sodium and potassium channel blocking properties and blocks these channels in all phases of the action potential (8). The unique pharmacological profile of vernakalant addresses many problems of existing anti-fibrillatory drugs by selectively targeting ion channels that are expressed primarily in atrial cardiomyocytes and provides rapid, effective treatment for acute onset AF.

Acute onset AF implies (for the purpose of this policy) a duration of less than 48 hours. Vernakalant is licensed for the rapid conversion of recent-onset AF to sinus rhythm in adults who are non-surgery patients with AF ≤ 7 days duration or post-cardiac surgery patients with AF ≤ 3 days duration (9). But for reasons of clarity, safety and efficacy (in terms of thromboembolic risk, uncertainty over duration of AF and effectiveness), the majority of post-marketing use has centred around those with a clear onset of symptoms and AF of ≤ 48 hours duration.

1.2 Scope

This policy applies to the use of vernakalant, a sodium and potassium channel blocking anti-arrhythmic drug. This is licensed for pharmacological cardioversion of

acute onset AF. This is to be within 48 hours of AF onset. If there are doubts over the duration of AF, traditional therapies should be followed and vernakalant should not be administered. The European Society of Cardiology recommend vernakalant in the treatment algorithm of acute onset AF (Appendix 1).

There are strict criteria for those who can receive vernakalant and the checklist (Appendix 2) must be adhered to. There are other groups in whom administration should be used with caution, but are not contra-indications (Appendix 3).

Prior to administration, the Consultant Cardiologist or Arrhythmia Nurse Specialist should may be contacted for discussion / review. With As experience, grows, Consultants and senior middle grades in the Emergency Department, Anaesthetics, Medicine and the Cardiology medical team may initiate vernakalant infusion. Otherwise out of hours, the decision should be discussed with the on-call medical middle grades. ("Out of hours" there is a middle grade in the Emergency Department until 2am).

Vernakalant must be given in a monitored environment and the protocol (Appendix 4) used prior to and alongside the infusion. This provides guidance on who can and cannot receive the infusion within the checklist (Appendix 2 and 4) and onward monitoring. When to stop or continue the infusion is also detailed, as is the treatment of adverse signs.

The Emergency Department is a suitable environment as is the High Dependency Unit and Intensive Care Unit. Telemetry monitoring is not appropriate and the care provider must be in attendance throughout the infusion and for at least 15 minutes after the infusion has finished. This is to ensure close monitoring and observation of the patient. The patient should be further monitored via continuous cardiac monitoring for 2 hours on completion of the infusion and if any adverse signs have occurred, until the patient is stable and vital signs and cardiac monitoring returned to baseline.

Documentation must be in accordance with usual standards and records will be accessed by the Arrhythmia Nurse (if not in attendance) for audit purposes. The Arrhythmia Nurses should be informed of the patients receiving vernakalant for audit.

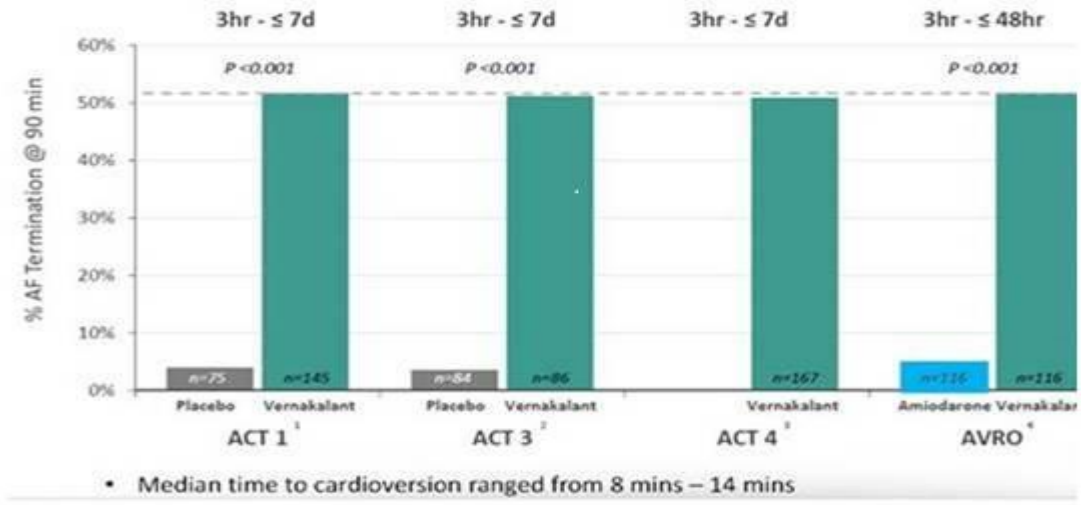
1.3 Principles

Management of AF can follow a rate or rhythm control approach. This decision is multi-factorial but is largely based on presentation and symptomatology. In acute onset AF, cardioversion is often selected and this can be with medications (pharmacological cardioversion) or electricity (direct current cardioversion).

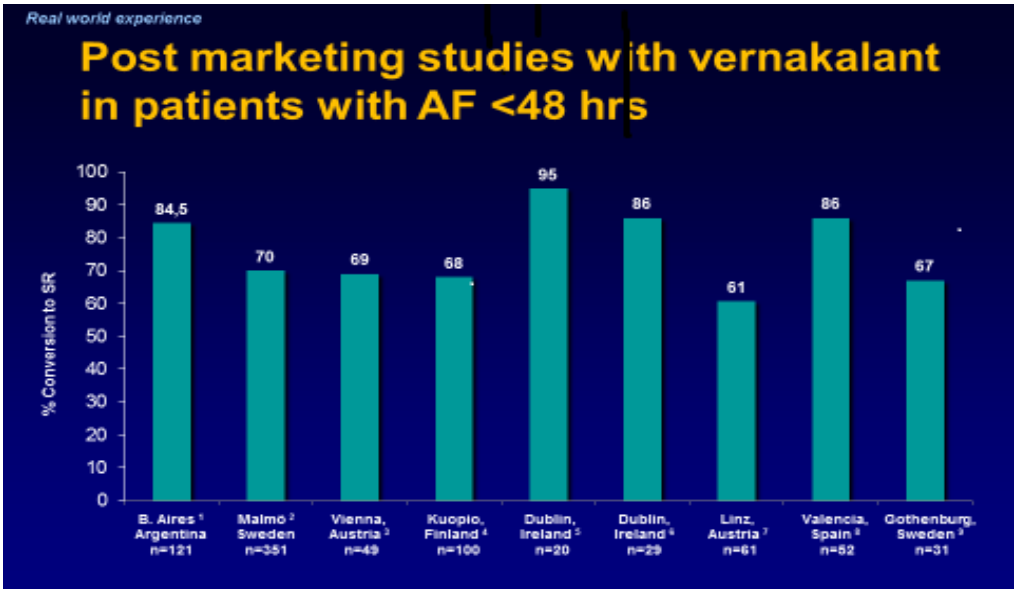
Due to limitations in existing therapies, vernakalant has been produced as an alternative with evidently efficient and effective outcomes as an option for pharmacological cardioversion. A summary of clinical trials can be seen in Appendix 5. In brief, ACT I and III showed vernakalant to be significantly more effective than placebo in converting AF (51.7% vs 4% and 51.2% vs 3.6%, respectively) (10,11). ACT IV demonstrated the restoration of sinus rhythm in 50.9% within 14 minutes

after starting the infusion (12). ACT II studied post-cardiac surgery AF patients and 47% patients converted within 90 minutes of the start of treatment with a median conversion time of 12 minutes (13). AVRO compared vernakalant to amiodarone and 51.7% of subjects converted within 90 minutes compared to 5.2% treated with amiodarone (14). In the pooled analysis, vernakalant was 8.4% more likely to convert AF to sinus rhythm than placebo or amiodarone without excess risk of adverse events (15). A further report highlighted over 95% of patients who converted to sinus rhythm after vernakalant treatment, remained in sinus rhythm at 24 hours (16). Figure 1 depicts cardioversion efficacy of vernakalant in phase 3 trials.

Figure 1.



Post marketing studies have identified even higher numbers who successfully cardiovert with vernakalant infusion when targeting only those with acute onset (≤48 hours duration). Conversion was as high as 95% (17). The aforementioned studies generally included patients with a longer AF duration.



A real world study included patients with AF onset ≤48 hours and 84.5% of patients converted to sinus rhythm with a mean time to conversion at 9 minutes (18). A retrospective registry found the median conversion time to be 11 minutes with 76% of patients converting to sinus rhythm when AF duration was ≤10 hours (19). A retrospective single centre, single arm study reported 86% successful cardioversion with vernakalant and a median time of conversion at 8 minutes (20). When comparing vernakalant to flecainide, cardioversion was achieved in 67% of the vernakalant group versus 46% in the flecainide group. Patients in the vernakalant group were older with more co-morbid risks (yet there was no difference in complication rates) (21). An earlier study also compared flecainide to vernakalant with time to conversion of 163 minutes with flecainide versus 10 minutes with vernakalant (22). Vernakalant was compared to electrical cardioversion in a retrospective study and the vernakalant group achieved sinus rhythm in 66.5% of patients compared to 94% in the electrical cardioversion group (23). But, the patients in the vernakalant group were discharged home sooner with lower rates of AF recurrence at one year follow up (23).

2. POLICY PURPOSE

The purpose of this policy is to provide guidance and criteria for the appropriate patient selection, administration, monitoring and follow up when receiving vernakalant. The protocol is provided here (Appendix 4) alongside supporting documentation pertinent to the administration of vernakalant.

2.1 Patient selection

Adults (> 18 years) with acute onset AF (≤ 48 hours) are eligible to receive vernakalant, who fulfil the appropriate criteria on the checklist (Appendix 2 and 4). If there is any doubt, patients must not receive vernakalant and instead, other means of rate or rhythm control should be selected.

Contraindications include hypotension <100mmHg, recent (<30 days) acute coronary syndrome (NSTEMI, STEMI, unstable angina), NYHA class III and IV heart failure, severe aortic stenosis, QT interval prolongation (uncorrected QT at baseline >440ms), severe bradycardia, a history of second or third degree AV block in the absence of a pacemaker and in conjunction with intravenous class I and III antiarrhythmic drugs administered within 4 hours.

If there is uncertainty regarding the onset of AF or vague symptoms, vernakalant must not be administered.

As per the protocol (Appendix 4), an echocardiogram should / must be performed before starting the infusion (if not already done within 1 year and clinically the patients presentation has not changed). This can be by contacting the Clinical Investigation Department where a physiologist will attend or by another competent practitioner. Chest auscultation identifying heart sounds is useful for those experienced in identifying murmurs indicative of valvular abnormalities. Baseline ECG is necessary to ensure there are no underlying conduction abnormalities or recent, undiagnosed acute coronary syndrome within the last 30 days.

2.2 Preparation and administration

Patients must have baseline observations recorded. Pre-existing hypotension or bradycardia can be identified, which may deem that patient unsuitable for vernakalant. Patients should be adequately hydrated and haemodynamically optimised and if applicable, anticoagulated. All patients will receive a single dose of low molecular weight heparin (e.g. enoxaparin) at treatment dose (1.5mg/kg) unless there are contraindications to this. All patients must then be assessed using the CHA^2DS^2-VASc stroke / thromboembolism risk stratification tool (Appendix 6) and where there is a score of ≥1, patients should be anticoagulated with a direct oral anticoagulant (DOAC). Current formulary provides apixaban, dabigatran and rivaroxaban. Four weeks prescription should be provided and within this time, the patient will have follow up with the Arrhythmia Clinic.

Where possible, hypotension can be treated with intravenous fluids in order to qualify the patient as haemodynamically stable and therefore eligible to receive vernakalant.

Serum potassium levels must be checked and corrected to >3.5mmol/L prior to administration of vernakalant.

The patient must not have received any intravenous antiarrhythmic (class I and III) drugs within 4 hours prior to giving vernakalant, nor can they receive an alternative antiarrhythmic (class I or III) 4 hours after. Vernakalant is not recommended even when the patient has received a class I or III intravenous antiarrhythmic 4-24 hours prior to vernakalant due to lack of data.

Vernakalant must not be mixed with other medicinal products other than diluents glucose 5% or sodium chloride 0.9%.

Vernakalant is available and supplied as sterile concentrate containing vernakalant hydrochloride 20mg/ml. It must be diluted prior to administration to produce a solution with a concentration of 4mg/ml. Suitable diluents include 0.9% sodium chloride for injection or 5% glucose for injection. Vernakalant is available as 500mg/25ml vials and the number needed to prepare the appropriate quantity of solution will depend on the patient's weight. The infusion must not be given by hand or bolus injection. An infusion pump must be used to ensure safe delivery of the desired amount.

1st infusion: The total dose is 3mg/kg over 10 minutes (when body weight is ≥ 40kg and < 113kg). When the weight is ≥ 113kg, the total dose is 339mg (84.7ml of 4mg/ml solution) over 10 minutes.

If conversion to sinus rhythm has not occurred during this infusion, or if atrial flutter has resulted, continue until the end of the initial infusion. Monitor then for 15 minutes. If AF remains or if atrial flutter is still or becomes evident, continue on to administering the 2nd infusion.

2nd infusion: The total dose is 2mg/kg over 10 minutes (when body weight is ≥40kg and <113 kg). When the weight is ≥ 113kg, the total dose is 226mg (56.5ml of 4mg/ml solution) over 10 minutes.

2.3 Side effects and adverse signs

The most common side effects are minor and include sneezing, dysgeusia (taste disturbance) and paraesthesia and in the studies were transient and rarely treatment limiting. A full profile of system related side effects are listed in Box 1.

If any of the following signs or symptoms occur, the administration of vernakalant should be discontinued and patients should receive appropriate medical management. Discontinuing vernakalant may improve vital signs alone.

- A sudden drop in blood pressure or heart rate, with or without symptomatic hypotension or bradycardia
- Hypotension
- Bradycardia
- ECG changes (such as 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.

Box 1 Adverse reactions to vernakalant

Nervous system disorders	*Very common*: Dysgeusia *Common*: Paraesthesia; dizziness; headache, hypoaesthesia *Uncommon*: Burning sensation; parosmia; somnolence; vasovagal syncope
Eye disorders	*Uncommon*: Eye irritation; lacrimation increased; visual impairment
Cardiac disorders	*Common*: Bradycardia (often at the time of conversion from AF to sinus rhythm); atrial flutter (more common within 2 hours of receiving vernakalant) *Uncommon*: Sinus arrest; complete AV block; first degree AV block; left bundle branch block; right bundle branch block; ventricular extrasystoles; palpitations; sinus bradycardia; ventricular tachycardia; ECG QRS complex prolonged; ECG QT prolonged, cardiogenic shock
Vascular disorders	*Common*: Hypotension *Uncommon*: Flushing; hot flush; pallor

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

2.4 Monitoring

Monitor the patient's observations (blood pressure, pulse, oxygen saturations, respirations) every 5 minutes during the infusion and for at least 15 minutes after completion of vernakalant.

Continuous cardiac monitoring must be attached at all times. Remote telemetry monitoring is not sufficient. The patient must be observed at all times during the entire monitoring period whilst the infusion is running and for at least 15 minutes after. The patient should be further monitored for 2 hours after the start of infusion and until clinical and ECG parameters have stabilised.

2.5 Further management

If AF or atrial flutter remains after the second infusion, alternative management will follow. This may include accepting the arrhythmia and ensuring rate control. Beta blockers can be administered without waiting the 4 hours as necessary with alternative intravenous antiarrhythmics. Oral antiarrhythmic maintenance therapy can be resumed or initiated 2 hours after administration of vernakalant. Anticoagulation must still be considered as previously mentioned.

Electrical cardioversion may be required but studies have not included electrical cardioversion within 2 hours of vernakalant within their cohort so outcomes are not known. Normal procedures should apply when performing electrical cardioversion (e.g. general anaesthetic and safe, synchronised defibrillation).

2.6 Follow up

All patients who receive vernakalant must be referred to the Arrhythmia Nurse Specialist for Arrhythmia Clinic review and auditing purposes. Further assessment and management can then be made including the need for ongoing or initiation of anticoagulation.

3. CORPORATE PROCEDURE

This policy will be available for HSSD HCS staff to refer to on hssnet. It is intended for use by medical colleagues trained and competent in the safe prescription, administration and monitoring of patients deemed suitable to receive vernakalant. A member of the Cardiology team should may be notified of the impending suggestion of use and either the Consultant Cardiologist, Cardiology Staff Grade Senior Cardiology Clinical Fellow or Arrhythmia Nurse Specialist will attend if necessary (when at all possible).

As experience and competence continues to grow, use may be granted without the specialists attendance or review, but patient selection must be in accordance with the licensing agreements and checklist (Appendix 2).

4. DEVELOPMENT AND CONSULTATION PROCESS

Name and Title of Individual	Date Consulted
Dr Andrew Mitchell, Consultant Cardiologist	5.7.16
Dr Ranji Thomas, Associate Specialist, Cardiology	5.7.16
Dr Simon Chapman, ED Consultant	5.7.16
Dr Alan Thompson, Anaesthetics Consultant	9.7.16
Debbie O'Driscoll, Senior Pharmacist	9.7.16

Policy update, October 2019

Name and Title of Individual	Date Consulted
Dr Andrew Mitchell, Consultant Cardiologist	17.10.19
Dr Pierre Le Page, Consultant Cardiologist	17.10.19
Dr Chris Edmond, Cardiology Staff Grade	17.10.19, 9.12.19
Dr Simon Chapman, ED Consultant	11.11.19, 7.12.19
Debbie O'Driscoll, Senior Pharmacist – referred to Sarah Jane Burton, Pharmacist	11.11.19

5. AUDIT

Audit will be ongoing. Key audit criteria will include:

- Patient demographics
- Duration of AF
- History of arrhythmia (e.g. paroxysmal, new onset)
- Vital signs at baseline, during infusion and subsequent monitoring
- ECG at baseline and on completion (e.g. QT intervals)

- Rhythms and heart rate during infusion
- Adverse signs (and subsequent management)
- Side effects
- Rate of conversion (e.g. first or second infusion, minutes)
- Total time in hospital
- Management if conversion unsuccessful
- Patient satisfaction

6. REFERENCE DOCUMENTS

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Please also see further references for an overview of vernakalant with additional evidence:

Hall, A and Mitchell, A. (2019). Introducing vernakalant into clinical practice, Arrhythmias and Electrophysiology Review, 8(1), 70-74. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6434499/

Hall, A. (2018). Implementing vernakalant: a novel approach to cardioversion, Emergency Nurse, 27(1), 14-20. https://journals.rcni.com/emergency-nurse/evidence-and-practice/implementing-vernakalant-a-novel-approach-to-cardioversion-en.2018.e1902/print/abs

7. IMPLEMENTATION PLAN

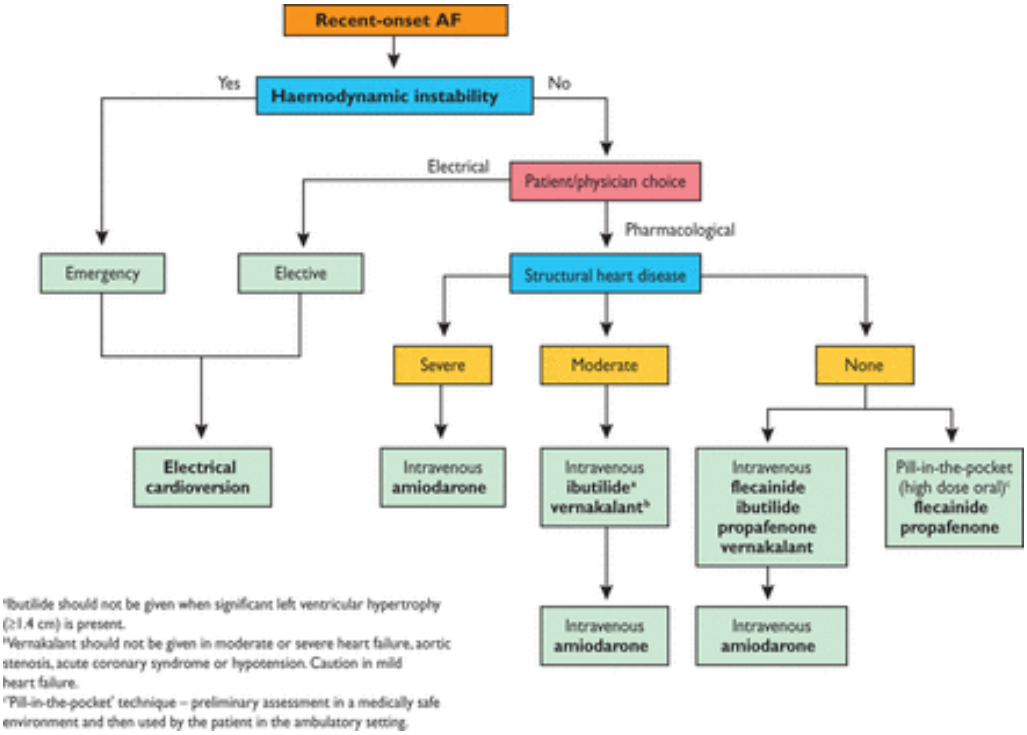
Action	**Responsible Officer**	**Timeframe**
Approval by Dr Mitchell, Consultant Cardiologist	Angela Hall	Mid July
Share with Cardiology team	Angela Hall	End July
Educate Emergency Department and disseminate policy and protocol	Angela Hall	End July
Sign off / ratification in Cardiology Governance meeting	Angela Hall	Next meeting
Send to HSSnet for uploading	Angela Hall	After Governance

Action	Responsible Officer	Timeframe
Approval by consultation team	Angela Hall	End October
Share with Cardiology team	Angela Hall	End October
Update Emergency Department and re-disseminate policy and protocol	Angela Hall	Next Governance meeting

8. APPENDICES

Appendix 1

Algorithm for Management of Acute Onset AF



[a]Ibutilide should not be given when significant left ventricular hypertrophy (≥1.4 cm) is present.
[b]Vernakalant should not be given in moderate or severe heart failure, aortic stenosis, acute coronary syndrome or hypotension. Caution in mild heart failure.
[c]'Pill-in-the-pocket' technique – preliminary assessment in a medically safe environment and then used by the patient in the ambulatory setting.

Management of AF – updated guidelines (2012, 2016)
European Society of Cardiology (24, 25).

Appendix 2

Checklist prior to administration of Vernakalant

CHECKLIST

12 lead ECG ☐

Echocardiogram (if not within 1 year or a change in clinical presentation) ☐

BRINAVESS (Vernakalant) must NOT be given to any patients with a "YES" response below:		
Does the patient have heart failure class NYHA Ill 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 msec)?	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 Ill) 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 drugs for at least 4 hours after infusion of BRINAVESS.		

Appendix 3

Cautions when considering administration of Vernakalant

Vernakalant should be used with caution in patients with:

- NYHA class I and II heart failure due to increased risk of hypotension and non-sustained ventricular arrhythmias.
- Vernakalant has not been evaluated in clinically significant valvular stenosis, hypertrophic obstructive cardiomyopathy or previously documented left ventricular ejection fraction ≤35%.

Clinical trial data is limited in these patients, hence vernakalant is not recommended. Patients with valvular heart disease should be monitored closely.

- Be aware if patients are taking background oral anti-arrhythmics. This was not an exclusion to study populations but numbers were limited. It is suggested that resumption or initiation of oral maintenance antiarrhythmic therapy is considered 2 hours following therapy with vernakalant.

Appendix 4 Local protocol for administration and management of Vernakalant

An anti-arrhythmic intravenous drug used for rapid conversion of recent-onset **atrial fibrillation** (AF) to sinus rhythm in adults

Refer to checklist (overleaf) for exclusion criteria

Please see attached drug information leaflet for further details

Continuous cardiac monitoring
Clinical area appropriate for cardioversion

New onset **AF** (≤ 48 hours)

CHECKLIST

If contraindications, use alternative

E.g. Enoxaparin 1.5mg/kg

Anticoagulate as necessary - CHA2DS2-VASc
LMWH stat, DOAC for at least 4 weeks if risk factors *

Ensure adequately hydrated and haemodynamically optimised

Correct potassium levels to ≥ 3.5mmol/l

Adverse signs (STOP infusion)
Sudden drop in BP / HR, hypotension, bradycardia, ECG changes (sinus pause, CHB, new BBB, prolongation of QT or QRS interval, ventricular arrhythmia, signs of infarction / ischaemia)
See over for management

Prepare Vernakalant according to weight
≤ 100kg: 25ml of Vernakalant 20mg/ml is added to 100ml of diluent
≥ 100kg: 30ml of Vernakalant 20mg/ml is added to 120ml of diluent

0.9% sodium chloride, or 5% glucose

1st infusion = 3mg/kg over 10 minutes (see dosage chart according to weight > or < 113kg)

Continuous cardiac monitoring
Close observation of vital signs

STOP infusion if adverse signs

End of 1st infusion

SR AF or changed to flutter

Continue cardiac monitoring / vital signs for at least 15 minutes post infusion
Further monitoring for 2 hours after start of 1st infusion and until clinical and ECG parameters are stable

If AF persists or changes to atrial flutter 15 minutes after 1st infusion, prepare and administer 2nd infusion (using the same infusion bag as for 1st infusion)
2nd infusion = 2mg/kg over 10 minutes (see dosage chart)

Discharge, refer to Arrhythmia Nurse
Ensure consideration of OAC

Continue as 1st infusion

End of 2nd infusion

SR – monitoring as above, post infusion.
Discharge, refer to Arrhythmia Nurse
Ensure consideration of OAC

AF persists or changes to atrial flutter – consider alternative management

Cardioversion

SR

AF

Risk factors

Y

4 weeks OAC

N

No long term OAC

Consider long term OAC
Follow up

Management of adverse signs (indications to stop the infusion)

Hypotension	E.g. systolic blood pressure <85mmHg or symptomatic May respond by stopping vernakalant infusion Non-pharmacological manoeuvers e.g. trendelenburg bed position Intravenous fluids e.g. 500ml 0.9% sodium chloride. Review and titrate according to response Ephedrine (30mg/ml) IV bolus dilute 1ml to 10ml 0.9% sodium chloride. Dose usually 1ml of diluted solution over 1 minute. Wait few minutes for response, if inadequate, repeat. No more than 9mg normally needed
Bradycardia	E.g. heart rate <40bpm or sinus pause ≥5 seconds May respond by stopping vernakalant infusion Atropine 600micrograms IV bolus, titrate according to response. 3mg total vagal blockade
VT	Pulseless – ALS procedures. Defibrillation With a pulse - magnesium 2g IV bolus (when VT and urgent correction needed). Dilute each ml of magnesium sulfate 50% with 1.5ml 0.9% sodium chloride or 5% glucose. Can be further diluted to a convenient volume and administered over 10 minutes.

QRS widening by > 50% or new bundle branch block
QTc prolongation by 25% from baseline or to >550ms
Complete heart block

May respond by stopping vernakalant infusion
If complete heart block is causing haemodynamic compromise consider externally pacing, IV isoprenaline infusion, temporary pacing wire and referral to senior doctor in Cardiology

Drug treatments as per University College London Hospitals NHS Guide on Injectable Medicines (2010). 3rd edition.

Appendix 5

Summary of clinical trials relating to Vernakalant

Study	Design	Number of patients	Underlying heart disease	AF duration	Time to conversion (median), minutes	Conversion to sinus rhythm vs. placebo or control (primary endpoint*)	Other efficacy outcomes
CRAFT[119]	Double-blind, dose-ranging, placebo-controlled, phase II	56 Vernakalant 2 + 3 mg/kg: *n* = 18; Vernakalant 0.5 + 1 mg/kg: *n* = 18 Placebo: *n* = 20	Hypertension, 57%; diabetes, 23%	AF 3–72 h (mean, 11.5–19.5 h)	14	61% (vernakalant 2 + 3 mg) vs. 5%, *P* <0.001	Conversion rate for vernakalant 0.5 + 1 mg/kg: 11%
ACT I[120]	Double-blind, placebo-controlled, phase III	336 Vernakalant: *n* = 221 Placebo: *n* = 115	Hypertension, 42.5%; ischaemic heart disease, 20.2%; myocardial infarction, 9.8%; heart failure, 14.9%; diabetes, 8%	AF 3 h–45 days (median, 41.8–59.1 h) AF 3 h–7 days (median, 28.2–28.4 h): *n* = 220 AF 8–45 days (median, 19.4–25.5 days): *n* = 116	11	51.7% vs. 4%, *P* <0.001	76% converted after a single dose. Conversion rates for patients with AF ≤48 h: 62.1% vs. 4.9%, *P* <0.001; with AF >7 days: 7.9% vs. 0%, *P* = 0.09
ACT II[122]	Double-blind, placebo-controlled, phase III	160 Vernakalant: *n* = 106 Placebo: *n* = 54	CABG, 67%; valvular surgery, 23.6%; combined, 9.3%. Hypertension, 69.5%; ischaemic heart disease, 80%; heart failure, 31.6%	AF 3–72 h between 24 h and 7 days after cardiac surgery Atrial flutter: *n* = 10	12	47% vs. 14%, *P* <0.001	75% converted after a single dose. Patients with flutter converted: 0/6 vs. 1/4
ACT III[121]	Double-blind, placebo-controlled, phase III	265 Vernakalant: *n* = 134 Placebo: *n* = 131	Hypertension, 43.9%; ischaemic heart disease, 11.8%; myocardial infarction, 6.5%; heart failure, 19.8%; diabetes, 8.4%	AF 3 h–45 days AF 3 h–7 days: *n* = 172 AF 8–45 days: *n* = 70 Atrial flutter: *n* = 23	8	51.2% vs. 3.6%, *P* <0.001	81.8% converted after a single dose. Conversion rates for patients with AF >7 days: 9% vs. 3%, *P* = 0.33; with flutter: 7.1% (1/14) vs. 0% (0/9)
ACT IV[123]	Open-label, phase IV	167	Hypertension, 44%; ischaemic heart disease, 8%; heart failure, 11%	AF 3 h–45 days (median, 38.5 h) AF 3 h–7 days: *n* = 170 AF 8–45 days: *n* = 69	14	50.9%	Conversion rates for patients with AF ≤48 h: 57.9%; with AF >7 days: 11.6%
AVRO[124]	Double-blind, active-controlled (i.v. amiodarone), phase III	232 Vernakalant: *n* = 116 Amiodarone: *n* = 116	Hypertension, 71.6%; ischaemic heart disease, 22.4%; myocardial infarction, 8.2%; heart failure, 19.8%, (NYHA I, 45.7%, NYHA II, 54.3%); valvular heart disease, 6.9%	AF 3–48 h (median, 17.7 h)	11	51.7% vs. 5.2%, *P* <0.0001	Reduction in symptoms at 2 h reported by 53.4% patients in the vernakalant group vs. 32.8% in the amiodarone group, *P* = 0.0012
Scene 2[129]	Double-blind, controlled, phase II/III	54 Vernakalant: *n* = 39 Placebo: *n* = 15	–	Atrial flutter 3 h–45 days (mean, 98–178 h)	–	3% vs. 0%, *P* = 0.45	–

(10, 11, 12, 13, 14, 24)

Appendix 6

CHA2DS2-VASc Stroke / Thromboembolic Risk Stratification Tool

	Condition	Points
C	**Congestive heart failure** (or LV dysfunction)	1
H	**Hypertension** BP>140/90 or treated hypertension on medication	1
A_2	**Age** ≥ 75 years	2
D	**Diabetes Mellitus**	1
S_2	**Prior Stroke** or **TIA** or **Thromboembolism**	2
V	**Vascular disease** (e.g. MI, PVD, Aortic plaque)	1
A	**Age 65-74 years**	1
S_c	**Sex category** (female gender)	1

Treat a score of ≥1 with 4 weeks anticoagulant until further review (unless there are contraindications for doing so e.g. allergy, profound clotting disorders).