Ajmaline provocation for suspected Brugada syndrome

Classification: Procedural Guideline
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Who should read this document?

Senior and middle-grade medical staff in the Cardiology department.

Key Messages

This protocol is intended to reveal the characteristic ECG abnormalities of Brugada syndrome (BrS) in patients in whom the need exists to exclude or confirm this diagnosis. This is a highly specialist investigation, and should only be performed on the Heart Care Unit by a member of the senior or middle-grade cardiology medical staff on the recommendation of a consultant cardiologist.

Background & Scope

The objective of this protocol is to determine whether a Brugada pattern can be induced and therefore whether a diagnosis of BrS can be made in patients with suspected BrS. Patients with suspected BrS can be divided in 4 groups (4 main indications):

1) Survivors of cardiac arrest with structurally normal heart and no evidence of other channelopathy
2) Evidence of runs of polymorphic VT in patients with structurally normal heart and no evidence of other channelopathy
3) Screening of family members of patients with BrS or unexplained sudden death
4) Patients with type II and III Brugada ECG patterns

What’s new in this version?

Updates to rate of administration of Ajmaline changed from 10mg over 30 seconds to 10mg over 1 minute.

Updates to isoprenaline sulfate dosing and administration guidance, including Appendix 3.
Pre-Test Check List

Before beginning the ajmaline provocation procedure the pre-test check list must be completed (see protocol pro-forma page 1 – in Appendix 1):

1. No contraindications to ajmaline provocation
   - Moderate LV systolic function or worse
   - Complete RBBB or LBBB
   - Myocardial infarction in past 3 months
   - Evidence of sinus node disease
   - 2\textsuperscript{nd}-degree AV-nodal block
   - Hypertrophic Cardiomyopathy
   - QT\textsubscript{C} prolongation (>450ms in men; >460ms in women)
   - Myasthenia gravis
   - Diagnostic Brugada pattern already present on ECG
   - Allergic to ajmaline

2. Medications stopped on day of test
   - If possible all medications should be avoided on the day of the test. Medications that impair conduction or prolong the QT interval should be avoided if at all possible (a list of drugs that prolong the QT interval is available at http://www.sads.org.uk/drugs_to_avoid.htm and in appendix 4). The test can be performed if medications have been taken, but risk of arrhythmia is higher.

3. Advanced Life Support facilities immediately accessible
4. U&E and LFTs satisfactory within last four weeks
5. No previous adverse reactions to ajmaline
6. Clear fluids only for 6 hours prior to test
7. Patient consented (very small risk of arrhythmogenesis)
8. Patient’s weight documented
9. Baseline heart rate, blood pressure and ECG documented
10. No Type 1 Brugada abnormalities on baseline ECG with high precordial leads (see protocol pro-forma page 2)
11. Venous access (green venflon) - choose a large vein.
12. Patient attached to bedside ECG monitor
13. Patient attached to SaO\textsubscript{2} probe
14. Ajmaline prescribed
15. Isoprotenerol (isoprenaline) and syringe pump available
Once the medical practitioner performing the protocol has confirmed in writing that all pre-test checks are satisfactory (on protocol pro-forma page 1), the test can be performed.

**Ajmaline Administration**

1. Draw up 20ml of 5mg/ml ajmaline solution (= 100mg ajmaline)
2. Perform pre-ajmaline ECG with high precordial leads (see diagram on protocol pro-forma page 2)
3. Inject 2ml (10mg) of ajmaline solution, IV, over 60 seconds followed by 5ml saline bolus. Monitor the injection site closely for phlebitis.
4. Wait 3 minutes, then repeat ECG with high precordial leads
5. If no ECG changes repeat steps 3 and 4 until the maximum dose of ajmaline has been administered (1mg/kg up to a maximum of 100mg) OR one termination criterion manifests

The patient may experience cutaneous flushing and eyelid twitching. Other side effects are rare.

**Termination Criteria:**

1. Diagnostic Brugada pattern in at least one ECG lead (see appendices 1 and 2)
2. Occurrence of ventricular ectopic beats or ventricular tachycardia
3. Sinus arrest
4. Bradycardia <50/min
5. 2nd or 3rd degree AV-nodal block
6. Prolongation of QRS duration by more than 30%

**Positive ECG criteria**

1. In the case of a negative baseline ECG, a J-wave of >2 mm absolute amplitude in any of the V₁ and/or V₂ leads, with or without RBBB, is considered positive.
2. Conversion of a type 2 or 3 Brugada ECG to a type 1 is considered positive. An increase in the J-wave amplitude of more than 2 mm without the development of a type 1 configuration is also considered significant, but is rarely observed.

**Ajmaline & Isoprenaline supplies from pharmacy**

As ajmaline & isoprenaline are both unlicensed medicines, the name of the patient, batch number of the drug and expiry date should all be recorded. This means when it is known a patient is to be admitted for this procedure then the ward pharmacist should be informed. The ward pharmacist will then dispense the required drugs for the individual patient.
Ajmaline will be dispensed as two 50mg/10ml ampoules
Isoprenaline sulfate will be dispensed as two 100micrograms/2ml ampoules.

Pharmacy will make the necessary documentation when dispensing these unlicensed medicines. The clinicians should follow the unlicensed policy and inform patients of the unlicensed status of the medicines being used.

Leaflets that explain the use of unlicensed medicines are also available in the unlicensed medicines policy.

**Post-test care:**

1. If test is negative (no Brugada ECG changes and no complications) patient can be discharged two hours after last dose of ajmaline was injected
2. If test is positive patient should remain on ECG monitor with hourly ECGs until changes resolve (this should take no more than 3 hours).
3. If test is positive and ventricular arrhythmias are observed:
   - Commence intravenous isoprenaline infusion (0.1mg isoprenaline /50ml Glucose 5%) at 0.002micrograms/kg/minute. The infusion rate should be increased every 5 minutes by increments of 0.002micrograms/kg/minute to achieve an increase in heart rate of 20% compared with the pre-infusion heart rate (maximum infusion rate = 1microgram/min ≡ 0.5ml/minute). See Table in Appendix 3 for detailed infusion guidance.
   - To prepare the above infusion – make up one 100microgram/2ml ampoule to total volume of 50mls with Glucose 5%. This will give a solution of concentration 2 micrograms per ml.
   - As an example – for an 80 KG patient the infusion would start at 0.002micrograms/kg/minute. This equates to 9.6micrograms/hr or 4.8mls/hr of the above 2 microgram/ml solution. This can be increased to a maximum rate of 30mls/hr for an 80 Kg patient. See Table in Appendix 3 for detailed infusion guidance.
   - The infusion should continue for 30 minutes once a 20% increase in heart rate or an infusion rate of 1microgram/min has been achieved.
   - Monitor ECG continuously and repeat 12-lead ECG with high precordial leads hourly until Brugada changes resolve.
   - Patients may be discharged four hours after isoprenaline infusion has finished if deemed clinically safe to do so.

4. A copy of the completed *pro forma* must be forwarded to Dr Paul Kingston in the cardiology department for audit purposes. The original document should be scanned for uploading onto the electronic patient record system.
Explanation of terms & Definitions

Brugada syndrome

Brugada syndrome is a rare inherited heart rhythm disturbance that restricts the flow of sodium ions into the muscle cells of the heart. As a result, the flow of electrical impulses through the heart is disrupted, which can lead to life-threatening heart rhythms.

Brugada syndrome more commonly affects young men of South East Asian descent. It is not a common condition in the western world, but those affected are mainly young to middle-aged men and some women.

References and Supporting Documents


http://www.brgada.org/about/about.html

http://www.nhs.uk/Conditions/brugada-syndrome/Pages/Introduction.aspx


Roles and responsibilities

This investigation should only be performed on the Heart Care Unit by a member of the senior or middle-grade cardiology medical staff on the recommendation of a consultant cardiologist.
Pre-Test Check List:

- No contraindications to ajmaline provocation
  - Moderate LV systolic function or worse
  - Myocardial infarction in past three months
  - 2nd-degree AV-nodal block
  - QTc prolongation (>450ms in men; >460ms in women)
  - Diagnostic Brugada pattern already present on ECG
  - Complete RBBB or LBBB
  - Evidence of sinus node disease
  - Hypertrophic cardiomyopathy
  - Myasthenia gravis
  - Allergic to ajmaline

- Medications stopped on day of test
  - If possible all medications should be avoided on the day of the test. Medications that impair conduction or prolong the QT interval should be avoided if at all possible (see appendix). The test can be performed if medications have been taken, but risk of arrhythmia is higher.

- Advanced Life Support facilities immediately accessible:
- U&E and LFTs satisfactory within last four weeks:
- No previous adverse reactions to ajmaline:
- List patient allergies:
- Clear fluids only for 6 hours prior to test:
- Patient consented (very small risk of arrhythmogenesis):
- Patient’s weight documented: _____________ kg
- Baseline heart rate, blood pressure and ECG documented:
- No Type 1 Brugada abnormalities on baseline ECG with high precordial leads (see overleaf):
- Venous access (green venflon) – choose a large vein:
- Patient attached to bedside ECG monitor:
- Patient attached to SaO₂ probe:
- Ajmaline prescribed:
- Isoproterenol (isoprenaline) and infusion pump available:

Proceed with test if all pre-test check list criteria are met.

Person confirming that test may be performed:

Name: ____________________ Signature: ____________________
Date: ____________________
Ajmaline provocation for suspected Brugada Syndrome - 2

<table>
<thead>
<tr>
<th>Name</th>
<th>Hospital Number</th>
<th>NHS Number</th>
<th>Date of Birth</th>
</tr>
</thead>
</table>

Patient weight =

Dose of ajmaline = 1mg/kg (up to maximum of 100mg) =

\[
\text{mg} \quad = \quad \text{ml}
\]

Ajmaline batch number: Expiry date:

**Ajmaline administration:**
1. Draw up 20ml of 5mg/ml ajmaline solution (= 100mg ajmaline)
2. Perform pre-ajmaline ECG with high precordial leads (see diagram)

3. Inject 2ml (10mg) of ajmaline solution, IV, over 60 seconds followed by 5ml saline bolus. Monitor the injection site closely for phlebitis.
4. Wait 3 minutes, then repeat ECG with high precordial leads
5. If no ECG changes repeat steps 3 and 4 until the maximum dose of ajmaline has been administered OR one termination criterion manifests

The patient may experience cutaneous flushing and eyelid twitching. Other side effects are rare.

**Termination Criteria:**
- Diagnostic Brugada pattern in at least one ECG lead (see page 4 and appendix)
- Occurrence of ventricular ectopic beats or ventricular tachycardia
- Sinus arrest (very unusual with ajmaline provocation)
- Bradycardia <50/min
- 2\textsuperscript{nd} or 3\textsuperscript{rd} degree AV-nodal block
- Prolongation of QRS duration by more than 30%
Patient weight =

Dose of ajmaline = 1mg/kg (up to maximum of 100mg) =

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<tr>
<td>100mg</td>
<td></td>
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</tr>
</tbody>
</table>

Name:   Signature:   Date:
Post-test care:

1. If test is negative (no Brugada ECG changes and no complications) patient can be discharged two hours after last dose of ajmaline was injected.

2. If test is positive (see below) patient should remain on ECG monitor with hourly ECGs until changes resolve (this should take no more than 3 hours).

3. If test is positive and ventricular arrhythmias are observed:
   - Commence intravenous isoprenaline infusion (0.1mg isoprenaline /50ml Glucose 5%) at 0.002micrograms/kg/minute. The infusion rate should be increased every 5 minutes by increments of 0.002micrograms/kg/minute to achieve an increase in heart rate of 20% compared with the pre-infusion heart rate (maximum infusion rate = 1microgram/min ≡ 0.5ml/minute). See Table in Appendix 3 for detailed infusion guidance.
   - To prepare the above infusion – make up one 100microgram/2ml ampoule to total volume of 50mls with Glucose 5%. This will give a solution of concentration 2 micrograms per ml.
   - As an example – for an 80 KG patient the infusion would start at 0.002micrograms/kg/minute. This equates to 9.6micrograms/hr or 4.8mls/hr of the above 2 microgram/ml solution. This can be increased to a maximum rate of 30mls/hr for an 80 Kg patient. See Table in Appendix 3 for detailed infusion guidance.
   - The infusion should continue for 30 minutes once a 20% increase in heart rate or an infusion rate of 1microgram/min has been achieved.
   - Monitor ECG continuously and repeat 12-lead ECG with high precordial leads hourly until Brugada changes resolve.
   - Patients may be discharged four hours after isoprenaline infusion has finished if deemed clinically safe to do so.

4. Ajmaline and isoprenaline are unlicensed medicines. Ensure that these medicines are ordered from pharmacy specifically for the individual patient for whom they are required.

5. The original document should be scanned for uploading onto the electronic patient record system. A copy of the completed pro forma must be forwarded to Dr Paul Kingston in the cardiology department for audit purposes.

Positive ECG criteria

1. In the case of a negative baseline ECG, a J-wave of >2 mm absolute amplitude in any of the V1 and/or V2 leads, with or without RBBB, is considered positive.

2. Conversion of a type 2 Brugada ECG to a type 1 is considered positive. An increase in the J-wave amplitude of more than 2 mm without the development of a type 1 configuration is also considered significant, but is rarely observed.
Appendix - Ajmaline provocation protocol for diagnosis of Brugada syndrome

This test must be performed on the Heart Care Unit

Indications

The objective of this protocol is to determine whether a Brugada pattern can be induced and therefore whether a diagnosis of Brugada syndrome (BrS) can be made in patients with suspected BrS. Patients with suspected BrS can be divided in 4 groups (4 main indications):

1) Survivors of cardiac arrest with structurally normal heart and no evidence of other channelopathy
2) Evidence of runs of polymorphic VT in patients with structurally normal heart and no evidence of other channelopathy
3) Screening of family members of patients with BrS or unexplained sudden death
4) Patients with type II and III Brugada ECG patterns

Pre-test preparation

Patients should be fasted for at least 6 hours. If possible they should stop all medications, especially medications that can worsen Brugada pattern (list available on brugadadrugs.org and in appendix 5). Consent patient, explain risk benefit (very small risk of arrhythmogenesis)

Test environment

Test should performed under continuous ECG monitoring and regular blood pressure monitoring. Personnel trained in advanced life support should be present. Advanced life support facilities should be available including:

- External defibrillator
- External pacemaker
- Intubation facilities
- Resuscitation drugs (especially isoprenaline and atropine).
ECG should ideally be performed using standard leads plus high precordial leads. The high precordial leads are recorded with electrodes located in 2\textsuperscript{nd} and 3\textsuperscript{rd} intercostal spaces at left and right sternal edges (“high” V\textsubscript{1} & V\textsubscript{2}). It is acceptable to forego the use of V\textsubscript{3} – V\textsubscript{6} if it proves technically difficult to obtain recordings from these ECG leads and from the high precordial leads at the same time (i.e. if 15-lead ECG is unavailable).

**Criteria for positive test**

A test is diagnostic for BrS when a type I pattern is induced in at least one lead between V\textsubscript{1}–V\textsubscript{2} and high precordial. The figure below is taken from a recent consensus conference and summarizes the definition of type I Brugada pattern.

---

**Type 1: coved pattern**

This typical coved pattern present in V\textsubscript{1}–V\textsubscript{2} the following:

a. At the end of QRS, an ascending and quick slope with a high take-off $\geq 2$ mm followed by concave or rectilinear downsloping ST.

b. There are few cases of coved pattern with a high take-off between 1 and 2 mm.

c. The high take-off often does not correspond with the J point (Fig. 4 B).

d. At 40 ms of high take-off, the decrease in amplitude of ST is $\leq 4$ mm.\textsuperscript{28} In RBBB and athletes, it is much higher.

e. ST at high take-off > ST at 40 ms > ST at 80 ms.

f. ST is followed by negative and symmetric T wave.

g. The duration of QRS is longer than in RBBB, and there is a mismatch between V\textsubscript{1} and V\textsubscript{6} (see text).

---

**Type 2: saddle-back pattern**

This typical saddle-back pattern present in V\textsubscript{1}–V\textsubscript{2} the following:

a. High take-off of r' (that often does not coincide with J point) $\geq 2$ mm.

b. Descending arm of r' coincides with beginning of ST (often is not well seen).

c. Minimum ST ascent $\geq 0.5$ mm.

d. ST is followed by positive T wave in V\textsubscript{2} (T peak $>$ ST minimum $>$ 0) and of variable morphology in V\textsubscript{1}.

e. The characteristics of triangle formed by r' allow to define different criteria useful for diagnosis (see above and text).

• $\beta$ angle.\textsuperscript{29}

• Duration of the base of the triangle of r' at 5 mm from the high take-off greater than 3.5 mm$^2$.

f. The duration of QRS is longer in BrP type 2 than in other cases with r' in V\textsubscript{1}, and there is a mismatch between V\textsubscript{1} and V\textsubscript{6} (see text).
## Appendix 3 – Isoprenaline dosing guidance

**Guidance for administration of isoprenaline infusion if it is required – doses only to be use as part of Ajmaline provocation protocol for Brugada syndrome.**

1. Make up one ampoule of isoprenaline sulfate (100mcg in 2ml) to 50mls using glucose 5%. This will give a concentration of 2micrograms/ml. (*Note Glucose should be used as isoprenaline sulfate is acidic*).

2. The 50mls solution should be administered using a syringe pump.

3. Use a starting dose of 0.002micrograms/kg/min and increase the infusion rate every 5 minutes by increments of 0.002micrograms/kg/min to achieve an increase in heart rate of 20% compared with the pre-infusion heart rate. See example infusion rates based on weight in the table below.

4. If the first 50mls is used and further infusion is required repeat from step 1 using the second available 100microgram in 2ml ampoule of isoprenaline.

5. Maximum infusion rate is 1microgram/min (or 0.5ml/min or 30mls/hr) – as indicated by the last infusion rate stated for each of the weights in the table below.

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<th>Dose mcg/kg/ min</th>
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<td>27</td>
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<td>to max 30mls/hr</td>
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</table>

*Rate mls/hr via syringe pump*
## Appendix 4 – Drugs that prolong the QT interval

This is a list of drugs that have been associated with a risk of prolongation of the QT interval. The risk is not the same with all drugs, but there is some risk of prolongation of the QT interval with all of these agents.

<table>
<thead>
<tr>
<th>Drug</th>
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<td>Adrenalin</td>
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<td>Methadone</td>
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Appendix 5 – Ajmaline – Summary of Product Characteristics

P015A
Patient Information Leaflet
Gilurytmal® 50 mg / 10 ml injection solution
Active substance: Ajmaline

Read the entire leaflet carefully before starting to take this medicine:
- Retain this leaflet as you may want to refer to it again later.
- Consult your doctor or pharmacist if you have any further questions.
- This medicine has been prescribed for you personally and should not be given to other people. It may harm them even if they have the same symptoms as you.
- If you are severely affected by one of the listed side effects or you notice side effects that are not mentioned in this leaflet, please tell your doctor or pharmacist.

This leaflet includes:
1. What is Gilurytmal 50 mg/10 ml and what is it for?
2. Before using Gilurytmal 50 mg/10 ml.
3. How to use Gilurytmal 50 mg/10 ml.
4. Possible side effects.
5. How to store Gilurytmal 50 mg/10 ml.
6. Further information.

1. What is Gilurytmal 50 mg/10 ml and what is it for?
This medicinal product is a class II anti-arrhythmic drug.
Gilurytmal is used for:
- Symptomatic and acute treatment for cardiac arrhythmia with increased heart rate (tachycardia) in the atrium of the heart (supraventricular) e.g.:
- AV-junctional tachycardia
- supraventricular tachycardia with WPW syndrome
- paroxysmal atrial flutter (intermittent arrhythmia)
- severe symptomatic ventricular tachycardia where the doctor deems this to be life-threatening.

2. Before using Gilurytmal 50 mg/10 ml.
Do not use Gilurytmal 50 mg/10 ml:
- If you are hypersensitive (allergic) to ajmaline or one of the other ingredients in Gilurytmal 50 mg/10 ml injection solution (see Section 6 Further information).
- With severe disturbances of A-V conduction (2nd and 3rd degree AV block).
- With pre-existing conduction disturbances within the ventricles (intraventricular).
- With Stokes-Adams attacks.
- With manifest weakness of the heart muscle (heart failure).
- With substantial increase in spread of stimulation in the ventricles (broadening of QRS complex) or prolongation of the overall electrical ventricular action (QT interval).
- With interactions with cardiac-acting glycosides (substances to promote contractility of the heart muscles).
- With myasthenia gravis (formation of antibodies against the body’s own substances resulting in disrupted transmission of stimulus from nerve to muscle).
- With pathological enlargement of the heart muscle (hypertrophic cardiomyopathy).
- With heart beating too slowly (bradycardia) (<50 beats/min.).
- With heart beating too fast (tachycardia) due to weakness of the heart muscle (cardiac decompensation).
- Within the first three months following myocardial infarction, or in patients with a left ventricular ejection fraction of less than 35% (exception: patients with potentially fatal ventricular arrhythmia).

If heart failure and cardiac arrhythmia occur together, the heart failure should be treated first as the cardiac arrhythmia may be due to the heart failure.

Take special care with Gilurytmal 50 mg/10 ml.
In patients with:
- Impaired liver function.
- Disorder of the body’s own pacemaker for the heart action (sick sinus syndrome).
- Milder disturbances of A-V conduction (1st degree AV block).
- Incomplete blockage of conductivity within the ventricles (incomplete bundle branch block).
- Low blood pressure (arhythmogenic hypotension < 90 mmHg systolic).
- Impaired rate of hepatic blood circulation (manifest weakness of the heart muscle, acute cardiac infarction, low blood pressure).

The dose must be adjusted accordingly.

Patients with renal dysfunction should only undergo careful treatment.
Intravenous use requires strict cardiological monitoring and should therefore only be carried out where appropriate resuscitation equipment and suitable monitoring facilities are available.
Ajmaline markedly raises the pacemaker stimulation threshold.

When administering as a drip it must be borne in mind that there are so-called poor metabolisers for ajmaline whereby ajmaline is metabolised more slowly. The incidence of this polymorphism is 7-8%.

Prolonged use may result in substantially higher plasma concentrations in these patients. If there is a deterioration in haemodynamic parameters or ECG parameters during an infusion, the infusion should be discontinued immediately.

Children
As there is insufficient data available on efficacy and safety with children, Ajmaline should not be used for children.

Taking Gilurytmal 50 mg/10 ml with other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken/used other medicinal products, including non-prescription medicines.

When ajmaline is combined with other anti-arrhythmics, beta-blockers (agent to block mediators in the sympathetic nervous system) or calcium antagonists (agents to treat angina pectoris and high blood pressure), an additive inhibitory effect on conduction from the atria to the ventricles (AV conduction), conduction within the ventricle (intraventricular) and conductivity is to be expected.

Ajmaline should not be combined with other Class I anti-arrhythmics due to the risk of onset of severe side effects.

Ajmaline exacerbates dose-related glycoside-induced conduction disturbances.

When ajmaline and quinidine are administered concomitantly, there is an increase in plasma levels of ajmaline and an increased effect on parts of the conduction system (His-Purkinje system).

Administration together with substances that increase enzyme activity (enzyme inducitors such as rifampin [anti-tuberculosis medication], phenobarbital, phenytoin, carbamazepine [anti-convulsant]) leads to acceleration of the breakdown of ajmaline in the liver, thereby substantially reducing plasma levels of ajmaline.

The incidence of persistent cholestasis (blockage of bile flow) increases with concomitant therapy with hormones, sulphonamides (including corresponding oral anti-diabetics), salicylates and diazepam.

Concomitant administration of medicinal products leading to a prolongation of QTC interval should be avoided due to potential onset of life-threatening cardiac arrhythmia (Torsade de pointes – tachycardia).

Ajmaline is partly metabolised by and inhibits cytochrome P450 isoenzyme CYP 2D6. Clinically significant interactions may occur between ajmaline and other substances that are metabolised by CYP 2D6 such as beta-blockers, antidepressants and neuroleptics. This must be particularly borne in mind when Gilurytmal is administered as an intravenous infusion (see dosage with daily and individual doses).

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking all medicines.

Pregnancy
Ajmaline should not be used during the first trimester of pregnancy as there is no data on reproductive toxicity from animal studies and also no references available on use during pregnancy.

Use of ajmaline in advanced pregnancy should only be considered in severe cases where the benefit to the mother outweighs the potential risk to the foetus. Theoretically, effects on the foetal heart and central nervous system may be possible so ajmaline should only be used during pregnancy where strictly indicated, where the patient can be under clinical observation and if the dose is reduced.

Breast-feeding
There is no data indicating that ajmaline passes into breast milk.
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Ajmaline provocation for suspected Brugada syndrome

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Check with Intranet that this printed copy is the latest issue

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Ability to drive and use machines
Ajmaline may impair the ability to drive and use machines especially at the start of treatment as well as when changing prescription and in conjunction with alcohol.

3. HOW TO TAKE Gilurymal 50 mg/10 ml
Gilurymal 50 mg/10 ml is not intended for repeated use.

Incompatibilities:
Gilurymal and furosemide i.v. are incompatible. The fall in pH value of the basic furosemide solution caused by the acidic ajmaline solution leads to flaky precipitations that may block a T-shaped tube.

In alkaline solutions (e.g. sodium hydrogen carbonate solution), precipitated occur, especially if the pH is increased. Thus, with a pH of 1.1 with a 4.2% sodium hydrogen carbonate solution, precipitation is observed after 24 hours.

Dosage:
Dosage and choice of pharmaceutical form essentially depend on a confirmed diagnosis.

The exact dosage must be set individually for each patient.
Adjusting the ant-arrhythmic with ventricular arrhythmia requires close cardiological in individual ECG technique. Appropriate cardiac monitoring and facilities for monitoring are available. During treatment, check-ups should be carried out at regular intervals (e.g. standard ECG, 24-hour ECG and, if necessary, exercise ECG). If there is a deterioration in individual parameters, e.g. prolongation of QRS interval or QT interval by more than 25% or of the PQ interval by more than 50% or a QT prolongation to more than 600 ms or an increase in number or severity of cardiac arrhythmia, therapy should be reviewed.

a) IV injection
Gilurymal should be slowly injected into a vein (intravenously) under ECG control. This applies especially for patients with a diseased heart muscle (dilatative cardiomyopathy). The rate of injection should not exceed 10 mg ajmaline/min. With pre-existing heart damage, the injection time of 50 mg should be extended to 15-20 minutes.

Intravenous injection should be carried out with facilities for defibrillation, intubation and resuscitation to hand (ready to externally restore the heart beat, insert a breathing tube through the mouth or nose into the airway to resuscitate). It is essentially recommended that haemodynamically stable (stable blood pressure, blood volume, etc.) arrhythmia is corrected under hospital conditions.

Max. single dose: 50 mg ajmaline (1 ampoule).

There is no need to continue the injection once the desired effect is achieved. If necessary, the injection can be repeated after 30 minutes. For controlled infusion, Gilurymal is suitable for administration using an automatic infusion syringe pump. Continuous ECG control is vital. A deterioration in individual ECG parameters (see above) may be a sign of too high a dose. The injection must then be temporarily or permanently ended.

b) Drip infusion
In cases of refractory tachycardic ventricular arrhythmia, it is possible to administer Gilurymal in the form of a drip infusion.

Therapeutic plasma levels of 0.4 g/ml to 2 g/ml have been measured following continuous infusion of 20 mg ajmaline/h to 50 mg ajmaline/h.

This results in the following dosage:
Initially, the infusion should be set at 20 mg/h (4 ml/h). If need be, the infusion can be increased up to a dosage of 50 mg/h (10 ml/h). Do not exceed the maximum dose of 1200 mg/24h.

The infusion should be set up under ECG control. This applies especially for patients with a diseased heart muscle (dilatative cardiomyopathy). Connection to an ECG monitor is necessary with longer infusions. A deterioration in individual ECG parameters (see above) may be a sign of too high a dose. The infusion must then be adjusted accordingly.

If there is a deterioration in haemodynamic parameters [Helen Taw] per ECG parameters during infusion with ajmaline, the infusion must be discontinued immediately.

Dosage for children and adolescents
As there is insufficient data on efficacy and safety in children, Gilurymal should not be used for children.

For patients with impaired liver function or decompensated heart failure, lower doses (10-30 mg/h) are sufficient due to reduced clearance (clearance of the relevant substance from plasma per unit of time).

Note:
Serum sodium levels should not exceed 145-150 mval (see Emergency measures).

Method and duration of use
Gilurymal is easily mixed with standard commercial neutral or acidic infusion solutions (e.g. Ringer’s lactate solution, full-strength electrolyte solutions, caloric solutions, etc.)

The duration of use depends on the pathological profile and is determined by the doctor.

When used it must be borne in mind that, to date, there has been no evidence for any Class I ant-arrhythmic that treatment of cardiac arrhythmia prolongs life.

If you use more Gilurymal 50 mg/10 ml than you should:
Symptoms typically only occur after an asymptomatic latent phase of 50-90 minutes.

Intoxications (toxic doses):
- Mild intoxications from 2 mg/kg
- Severe intoxications from 3 mg/kg
- Potentially fatal from 5 mg/kg

a) Signs (symptoms)
Reduction in the rate of depolarisation and cardiodepressive action can lead to numerous cardiovascular disorders:
- Low blood pressure (hypotension), cardiogenic shock, pulmonary oedema, excessive urge to urinate (oliguria) through to no urge to urinate (anuria)
- Slow heartbeat (bradycardia, conduction disorders: QRS broadening, intraventricular block, total conduction disturbances between atria and ventricles (total AV block), asystole
- Aggravation of tachycardic arrhythmia (e.g. also Torsade de pointes) through to ventricular flutter

b) Treatment of intoxications
Any episodes occurring after i.v. administration require immediate intensive monitoring.

For irregular rapid heartbeat (tachyarrhythmia), infusion of sodium as 1 molar solution over 2-3 minutes (e.g. NaCl solution, sodium bicarbonate solution, sodium lactate solution) at the following dosage:
Adults 100-160 mval, children, if necessary, 0.5-2 mval/kg body weight with control of sodium levels.

For irregular slow heartbeat (bradyarrhythmia) and for circulatory support, infusion of dopamine (2-10 µg/kg/min) or isoproterenol; for ventricular fibrillation or flutter, electroversion; for asystole, electrostimulation, temporary pacemaker or external heart massage, if necessary, early ventilation.

Haemoperfusion using XAD-4 is a relatively effective method for lowering plasma levels and more effective than carbon haemoperfusion.

Note:
Enzyme activities that may have risen during the acute intoxication phase may return to normal within 2-3 days.

If you have further questions on using the medicinal product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines Gilurymal 50 mg/10 ml can have side effects but these do not affect everyone. If you are severely affected by one of the listed side effects or you notice side effects that are not mentioned in this leaflet, please tell your doctor or pharmacist.

The following frequency criteria are used as a basis for evaluating side effects:

<table>
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<tr>
<th>Frequency</th>
<th>Description</th>
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<tbody>
<tr>
<td>Very frequent</td>
<td>More than 1 in 10 of those treated</td>
</tr>
<tr>
<td>Frequent</td>
<td>Fewer than 1 in 10 but more than 1 in 100 of those treated</td>
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<tr>
<td>Occasionally</td>
<td>Fewer than 1 in 100 but more than 1 in 1000 of those treated</td>
</tr>
<tr>
<td>Rarely</td>
<td>Fewer than 1 in 1000 but more than 1 in 10,000 of those treated</td>
</tr>
<tr>
<td>Very rarely</td>
<td>Fewer than 1 in 10,000 persons treated including isolated cases</td>
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</table>
6. FURTHER INFORMATION

What Gilurytmal 50 mg/10 ml contains
- The active substance is ajmaline
- The other ingredients are: phosphoric acid 84-80%, propylene glycol, water for injection, to adjust pH: sodium hydroxide.

What Gilurytmal 50 mg/10 ml looks like and contents of pack
Gilurytmal 50 mg/10 ml injection solution is a clear, colourless solution in glass ampoules (Type I clear glass as per Ph.Eur.)
Gilurytmal 50 mg/10 ml is available in the following pack sizes:
Pack of 5 x 10 ml ampoules (= 50 mg ajmaline)
Pack of 15 (3 x 5) x 10 ml ampoules (= 50 mg ajmaline)
Sample pack of 5 x 10 ml ampoules (= 50 mg ajmaline)
Not all pack sizes may be on sale.

Pharmaceutical distributor
CARINOPHARM GmbH
Bahnhofstraße 18
31008 Elze
Germany
Tel.: 0160 2 1234-01*  * €0.06 per call from German landline;
Fax: 0180 2 1234-02*  Max. mobile prices * €0.42 per minute
Email: info@carinopharm.de

Pharmaceutical manufacturer
Haupt Pharma Wülfing GmbH
Bethelner Landsstraße 18
31028 Gronau / Leine
Germany

Information last approved:
February 2010

5. HOW TO STORE  Gilurytmal 50 mg/10 ml

Store the medication out of the reach of children.

Do not use the product after the expiry date shown on the label and on the outer box. The expiry date refers to the last day of the month.

Storage conditions
Store the ampoules in the outer box to protect them against light.

Instructions on shelf life after opening or preparation
Once open, discard residues.
Discard discoloured solutions.
Dispose of unused medicinal products or waste material in accordance with national regulations.
Appendix 6 – Drugs to be avoided in patients with Brugada syndrome

Drugs to be avoided by Brugada Syndrome patients:

The following drugs have been associated with arrhythmias and the typical (type-1) Brugada syndrome ECG.

There are no randomized clinical studies in Brugada syndrome patients, therefore the level of evidence is mostly C (only consensus opinion of experts, case studies, or standard-of-care) and for some B (non-randomized studies).

Class I: There is evidence and/or general agreement that a given drug is potentially arrhythmic in Brugada syndrome patients.

Class IIa: There is conflicting evidence and/or divergence of opinion about the drug, but the weight of evidence/opinion is in favor of a potentially arrhythmic effect in Brugada syndrome patients.

Class IIb: There is conflicting evidence and/or divergence of opinion about the drug, and the potential arrhythmic effect in Brugada syndrome patients is less well established by evidence/opinion.

Class III: There is no or very little evidence and/or general agreement that a drug is potentially arrhythmic in Brugada syndrome patients.
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<tr>
<th>GENERIC NAME</th>
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<th>CLINICAL USE</th>
<th>REFERENCES</th>
<th>CLASS</th>
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<td>Antiarrhythmic Agent (1A: Na-blocker) / Arrhythmias</td>
<td>Brugada 1997, Rolf 2003, Wolpert 2005, Bébarová 2005</td>
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<td>Gilurytmal®</td>
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<td></td>
<td>Tambocor®</td>
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<td>Pilsicainide</td>
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<td>Antiarrhythmic Agent (1C: Na-blocker) / Arrhythmias</td>
<td>Takenaka 1999, Fujiki 1999, Takagi 2002, Kimura 2004</td>
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<tr>
<td></td>
<td>Sunrhythm®</td>
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<td>Procainamide</td>
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<td>Antiarrhythmic Agent (1A: Na-blocker) / Arrhythmias</td>
<td>Miyazaki 1996, Brugada 1997, Joshi 2007, Villemaire 1992</td>
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<td></td>
<td>Procan®</td>
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<td>Pronestyl®</td>
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<td>Rythmol®</td>
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## Psychotropic drugs

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<th>CLINICAL USE</th>
<th>REFERENCES</th>
<th>CLASS</th>
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<td>Amitriptyline</td>
<td>e.g. Elavil® Sarotex® Tryptizol®</td>
<td>Antidepressive (Tricyclic)</td>
<td>Bolognesi 1997 Rouleau 2001 Bebarta 2007 Nau 2000</td>
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<td>Clomipramine</td>
<td>e.g. Anafranil® Anafril®</td>
<td>Antidepressive (Tricyclic)</td>
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<td>Ila</td>
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<tr>
<td>Desipramine</td>
<td>e.g. Norpramin® Pentofran®</td>
<td>Antidepressive (Tricyclic)</td>
<td>Babaliaros 2002 Chow 2005 Akhtar 2006 Sudoh 2003</td>
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<tr>
<td>Lithium</td>
<td>e.g. Eskalith®</td>
<td>Antidepressive</td>
<td>Babalarios 2002 Darbar 2005 Wright 2010</td>
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<td>Loxapine</td>
<td>e.g. Cloxazepine® Loxitane® -other names-</td>
<td>Antipsychotic</td>
<td>Rouleau 2001 Kinugawa 1988</td>
<td>Ila</td>
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<tr>
<td>Nortriptyline</td>
<td>e.g. Nortrilen® Pamelor® -other names-</td>
<td>Antidepressive (Tricyclic)</td>
<td>Bardai 2013 Tada 2001 Muir 1982 Sudoh 2003</td>
<td>Ila</td>
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<td>Oxcarbazepine*</td>
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<td>Trifluoperazine</td>
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<td>Fluoperazine®</td>
<td>(Phenothiazine)</td>
<td>Klöckner 1987</td>
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<td>Stelazine®</td>
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### Anaesthetics/analgesics

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<th>CLINICAL USE</th>
<th>REFERENCES</th>
<th>CLASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>e.g.</td>
<td>Anesthetic / analgesic</td>
<td>Phillips 2003</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td>Marcaine®</td>
<td></td>
<td>Vernooy 2006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensorcaine®</td>
<td></td>
<td>Bramall 2011</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>De la Coussaye 1992</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Berman 1994</td>
<td></td>
</tr>
<tr>
<td>Procaine</td>
<td>e.g.</td>
<td>Analgesic</td>
<td>Arumugam 2012</td>
<td>IIa</td>
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<tr>
<td></td>
<td>Procaine-Penicillin</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Novocain®</td>
<td></td>
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</tr>
<tr>
<td>Propofol*</td>
<td>e.g.</td>
<td>Anesthetic</td>
<td>Inamura 2006</td>
<td>IIa</td>
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<tr>
<td></td>
<td>Diprivan</td>
<td></td>
<td>Vernooy 2006</td>
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<td></td>
<td></td>
<td></td>
<td>Robinson 2008</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Saint 1998</td>
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</table>

### Other substances

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>BRAND NAME®</th>
<th>CLINICAL USE</th>
<th>REFERENCES</th>
<th>CLASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>-Not</td>
<td>Cholinergic / Vasospastic / Intracoronary</td>
<td>Miyazaki 1996</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td>applicable-</td>
<td></td>
<td>Noda 2002</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Montgomery 1974</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>-Not</td>
<td>Other substances / Beverage</td>
<td>Shimada 1996</td>
<td>IIb</td>
</tr>
<tr>
<td>(overdose)</td>
<td>applicable-</td>
<td></td>
<td>Rouleau 2001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ohkubo 2013</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Habuchi 1995</td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td>-Not</td>
<td>Other substances / illicit drugs</td>
<td>Romero-Puche 2012</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>applicable-</td>
<td></td>
<td>Ghuran 2000</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Turkanis 1991</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>-Not</td>
<td>Other substances /</td>
<td>Littmann 2000</td>
<td>IIa</td>
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<td></td>
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</tr>
</tbody>
</table>
Drugs preferably to be avoided by Brugada Syndrome patients:

The following drugs have been associated with the typical (type-1) Brugada syndrome ECG. However, there is (as yet) no substantial evidence that these drugs can cause malignant arrhythmias in addition to inducing the ECG phenotype. This list includes drugs for which there is only experimental evidence (*in-vivo* or *in-vitro*) that suggests a possible deleterious effect in Brugada syndrome. Deleterious clinical effects have not been documented clearly and some patients may benefit from these drugs for other reasons. Nevertheless, it should be considered best practice to advise patients with Brugada syndrome to avoid these drugs or to use these drugs only after extensive consideration and/or in controlled conditions.

**Class I:** There is evidence and/or general agreement that a given drug is potentially arrhythmic in Brugada syndrome patients.

**Class Ila:** There is conflicting evidence and/or divergence of opinion about the drug, but the weight of evidence/opinion is in favor of a potentially arrhythmic effect in Brugada syndrome patients.

**Class Iib:** There is conflicting evidence and/or divergence of opinion about the drug, and the potential arrhythmic effect in Brugada syndrome patients is less well established by evidence/opinion.

**Class III:** There is no or very little evidence and/or general agreement that a drug is potentially arrhythmic in Brugada syndrome patients.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Applicable</th>
<th>Illicit Drugs / Anesthetic</th>
<th>Authors</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergonovine</td>
<td>e.g.</td>
<td>Vasospastic</td>
<td>Noda 2002</td>
<td>Iib</td>
</tr>
<tr>
<td>- Ergotrate®</td>
<td></td>
<td></td>
<td>Müller 1980</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-other</td>
<td>intracoronary</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- other names-</td>
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</tbody>
</table>
## Antiarrhythmic drugs:

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>BRAND NAME®</th>
<th>CLINICAL USE</th>
<th>REFERENCES</th>
<th>CLASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>e.g.</td>
<td>Antiarrhythmic Agent (class 3 - also 1A, 2, and 4 effects) / Arrhythmias</td>
<td>Chalvidan 2000, Paul 2006, D’Aloia 2012</td>
<td>Iib</td>
</tr>
<tr>
<td></td>
<td>Cordarone®</td>
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<tr>
<td>Disopyramide†</td>
<td>e.g.</td>
<td>Antiarrhythmic Agent (class 1A: Na-blocker) / Arrhythmias</td>
<td>Miyazaki 1996, Chinushi 1997, Shimizu 2000, Sugao 2005, Sumi 2010, Grant 2000</td>
<td>Iib</td>
</tr>
<tr>
<td></td>
<td>Dicorantil®</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Norpace®</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Ritmoforine®</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Disopyramide†</td>
<td>e.g.</td>
<td>Antiarrhythmic Agent (class 1A: Na-blocker) / Arrhythmias</td>
<td>Miyazaki 1996, Chinushi 1997, Shimizu 2000, Sugao 2005, Sumi 2010, Grant 2000</td>
<td>Iib</td>
</tr>
<tr>
<td></td>
<td>Dicorantil®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Norpace®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ritmoforine®</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lidocaine*</td>
<td>e.g.</td>
<td>Antiarrhythmic Agent (class 1A: Na-blocker) / Arrhythmias</td>
<td>Miyazaki 1996, Barajas 2008</td>
<td>Iib</td>
</tr>
<tr>
<td></td>
<td>Xylocaine®</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Inderal®</td>
<td></td>
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</tr>
<tr>
<td>Verapamil</td>
<td>e.g.</td>
<td>Antiarrhythmic Agent (class 4: Ca-blocker) / Arrhythmias</td>
<td>Miyazaki 1996</td>
<td>Iib</td>
</tr>
<tr>
<td></td>
<td>Covera®</td>
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</tbody>
</table>
† Disopyramide has been either suggested to be pro-arrhythmic or anti-arrhythmic in Brugada syndrome patients. The reason for these contradictory results is currently uncertain but could possibly include disparate underlying genetic defects. The Brugadadrugs.org Advisory Board advises caution and rigorous monitoring when using this drug to be able to react promptly to possible untoward effects.

* Lidocaine use for local anesthesia (e.g. by dentists) does seem to be safe when combined with adrenaline/epinephrine (e.g. xylocaine dental/epinephrine or articaïne/epinefrine (Ultracain® or Septanest® 1:100,000) and the amount administrated is low as it results in a local effect only. When applied on the skin it is also unlikely that there will be systemic effects, and will most probably be safe.

Psychotropic drugs:

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>BRAND NAME®</th>
<th>CLINICAL USE</th>
<th>REFERENCES</th>
<th>CLASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine*</td>
<td>e.g. Carbatrol®</td>
<td>Anticonvulsant Agent</td>
<td>Megarbane 2006</td>
<td>IIb</td>
</tr>
<tr>
<td>Clothiapine**</td>
<td>e.g. Clotiapine®</td>
<td>Antipsychotic Agent</td>
<td>Adler 2013</td>
<td>IIb</td>
</tr>
<tr>
<td>Cyamemazine</td>
<td>e.g. Cianatil®</td>
<td>Antidepressive Agent, Phenothiazine</td>
<td>Rouleau 2001, Crumb 2006</td>
<td>IIb</td>
</tr>
<tr>
<td>Drug</td>
<td>e.g.</td>
<td>Category</td>
<td>Author</td>
<td>Year</td>
</tr>
<tr>
<td>------------</td>
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<tr>
<td>Dosulepine</td>
<td>e.g. Dothiepin, Prothiaden, -other names-</td>
<td>Antidepressive Agent, Tricyclic</td>
<td>Meert 2010</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kiran 2010</td>
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</tr>
<tr>
<td>Doxepin</td>
<td>e.g. Sinequan®, Triadapin®, Zonalon®</td>
<td>Antidepressive Agent, Tricyclic</td>
<td>Bebarta 2007</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Muir 1982</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>e.g. Prozac®, Sarafem®, -other names-</td>
<td>Antidepressive Agent, SSRI</td>
<td>Rouleau 2001</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pacher 2000</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>e.g. Fevarin®, Luvox®, -other names-</td>
<td>Antidepressive Agent, SSRI</td>
<td>Stirmann 2009</td>
<td>IIb</td>
</tr>
<tr>
<td>Imipramine</td>
<td>e.g. Declomipramine®, Norfranil®, Tofranil®, -other names-</td>
<td>Antidepressive Agent, Tricyclic</td>
<td>Robert 1996</td>
<td>IIb</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>e.g. Lamictal®, -other names-</td>
<td>Anti-epileptic Agent, Bi-polar and depressive disorders</td>
<td>Chandra 2009</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Strimel 2010</td>
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<td></td>
<td></td>
<td></td>
<td>Rodrigues 2013</td>
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<td></td>
<td></td>
<td></td>
<td>Lang 1993</td>
<td></td>
</tr>
<tr>
<td>Maprotiline</td>
<td>e.g. Deprilept®, -other names-</td>
<td>Antidepressive Agent, Tetracyclic</td>
<td>Bolognesi 1997</td>
<td>IIb</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>e.g.</td>
<td>Antidepressive Agent, Tricyclic</td>
<td>Sawhney 2009</td>
<td>IIb</td>
</tr>
</tbody>
</table>
Ajmaline provocation for suspected Brugada syndrome

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Paxil®
Seroxat®
-other names-

Agent,
SSRI
Wang 2008
Yokota 1987

Perphenazine
e.g.
Perphenan®
-other names-

Antidepressive
Agent,
Phenothiazine
Bolognesi 1997
Bébarová 2009

Phenytoin
e.g.
Dilantin®
Diphantoine®
Epanutin®
-other names-

Anticonvulsant,
Antiarrhythmic
Agent
Al Aloul 2007
Xu 1991

Thioridazine
e.g.
Mellari®
Ridazine®
-other names-

Antipsychotic Agent
Copetti 2005

Anaesthetics/analgesics

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>BRAND NAME®</th>
<th>CLINICAL USE</th>
<th>REFERENCES</th>
<th>CLASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>e.g.</td>
<td>Anesthetic Agent</td>
<td>Rollin 2011</td>
<td>Iib</td>
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<tr>
<td></td>
<td>Esketamine®</td>
<td></td>
<td>Hara 1998</td>
<td></td>
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<tr>
<td></td>
<td>Ketanest®</td>
<td></td>
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<tr>
<td></td>
<td>-other names-</td>
<td></td>
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</tbody>
</table>

<p>| Tramadol     | e.g.        | Narcotic analgesic | Cole 2010 | Iib   |
|              | Ryzolt®     |              | Haeseler 2006 |       |
|              | Tramal®     |              |            |       |
|              | Zydol®      |              |            |       |
|              | -other names-|             |            |       |</p>
<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>BRAND NAME®</th>
<th>CLINICAL USE</th>
<th>REFERENCES</th>
<th>CLASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimenhydrinate</td>
<td>e.g.</td>
<td>Antiemetic Agent / Histamine H1 antagonist</td>
<td>Pastor 2001</td>
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<tr>
<td></td>
<td>Permital®</td>
<td></td>
<td>Kuo 2000</td>
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<tr>
<td>Diphenhydramine</td>
<td>e.g.</td>
<td>Histamine H1 antagonist</td>
<td>Lopez 2005</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Benadryl®</td>
<td></td>
<td>Kuo 2000</td>
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<td>Dimedrol</td>
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<tr>
<td>Edrophonium</td>
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<td>Cholinergic Agent</td>
<td>Miyazaki 1996</td>
<td>IIb</td>
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<td></td>
<td>Enlon®</td>
<td></td>
<td>Kasanuki</td>
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<td></td>
<td>Tensilon®</td>
<td></td>
<td>1997</td>
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<td>Indapamide</td>
<td>e.g.</td>
<td>Diuretic</td>
<td>Mok 2008</td>
<td>IIb</td>
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<tr>
<td></td>
<td>Idapamide®</td>
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<td>Lozol®</td>
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<tr>
<td>Metoclopramide</td>
<td>e.g.</td>
<td>Antiemetic Agent / dopamine antagonist</td>
<td>Bonilla 2011</td>
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<tr>
<td></td>
<td>Primperan®</td>
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<td>Wu 1992</td>
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<td>Reglan®</td>
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<tr>
<td>Terfenadine/ Fexofenadine</td>
<td>e.g.</td>
<td>Antihistamine</td>
<td>Matsuki 2009</td>
<td>IIb</td>
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<tr>
<td></td>
<td>Seldane®</td>
<td></td>
<td>DiDiego 2002</td>
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<td></td>
<td>Teldane®</td>
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<td></td>
<td>Allegra®</td>
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