SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Cardirest 50 tablets

Cardirest 100 tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cardirest 50: Each tablet contains 50 mg flecainide acetate.

Cardirest 100: Each tablet contains 100 mg flecainide acetate.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Cardirest 50: White to off-white, round shaped tablets, debossed "BPL025" on one side and plain on the other side.

Cardirest 100: White to off-white, round shaped tablets, debossed "BPL026" on one side and scored on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment with Cardirest should be initiated in a hospital for control of the following dysrhythmias:

- Sustained ventricular dysrhythmias.
- AV nodal reciprocating tachycardia; Wolff-Parkinson-White Syndrome and similar conditions with accessory pathway and anterograde or retrograde conduction.
- Paroxysmal atrial fibrillation in patients with disabling symptoms. Dysrhythmias of recent onset are more likely to respond.

In addition, Cardirest tablets are indicated in premature ventricular contractions and/or non-sustained ventricular tachycardia if these are causing disabling symptoms.

Cardirest tablets can be used for the maintenance of normal rhythm following conversion by other means.

4.2 Posology and method of administration

Posology

Supra-ventricular dysrhythmias: The recommended starting dosage is 50 mg twice daily and most patients will be controlled at this dose. If required, the dose may be increased to a maximum of 300 mg daily.

Ventricular dysrhythmias: The recommended starting dosage is 100 mg twice daily. The maximum daily dose is 400 mg daily and this is normally reserved for patients of large build or where rapid control of the dysrhythmia is required. After 3 – 5 days it is recommended that the dosage be progressively adjusted to the lowest level which maintains control of the dysrhythmia. It may be possible to reduce the dosage during long-term treatment.

Plasma levels:

Based on premature ventricular contractions (PVC) suppression, it appears that plasma levels of 200 – 1 000 ng/ml may be needed to obtain the maximum therapeutic effect. Plasma levels above 700 – 1 000 ng/ml are associated with increased likelihood of adverse experiences.

Special populations

Paediatric population

Cardirest is not recommended in children under 18 years of age, as there is insufficient evidence of its use in this age group.

Renal impairment

In patients with significant renal impairment (creatinine clearance of 35 ml/min/1.73 sq.m or less) the maximum initial dosage should be 100 mg daily (or 50 mg twice daily). When used in such patients, frequent plasma level monitoring is strongly recommended.

Elderly patients

The rate of flecainide elimination from plasma may be reduced in elderly people and doses may need to be adjusted accordingly.

Method of administration

Oral use.

4.3 Contraindications

Cardirest is contraindicated in:

- Hypersensitivity to flecainide or any excipients of Cardirest see section 6.1.
- Patients with cardiac failure, and in patients with a recent myocardial infarction or a history of myocardial infarction who have either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia.
- Pregnancy and lactation (see section 4.6).
- Patients with long standing atrial fibrillation and in patients with haemodynamically significant valvular heart disease. Unless pacing rescue is available, Cardirest should not be given to patients with

sinus node dysfunction, atrial conduction defects, second degree or greater atrio-ventricular block, bundle branch block or distal block.

- Cardirest is also contra-indicated in the presence of cardiogenic shock.

4.4 Special warnings and precautions for use

Increased mortality risk

Cardirest has been shown to increase mortality risk of post-myocardial infarction patients with asymptomatic ventricular dysrhythmia.

In post-myocardial infarction patients with asymptomatic ventricular dysrhythmia, oral flecainide was associated with a 2.2 fold higher incidence of mortality or non-fatal cardiac arrest as compared with its matching placebo. An even higher incidence of mortality was observed in flecainide-treated patients with more than one myocardial infarction.

There is no evidence that the use of Cardirest favourably affects survival or the incidence of sudden death.

Structural Heart Disease

Cardirest should be avoided in patients with structural organic heart disease or abnormal left ventricular function.

Effects on Pacemaker Thresholds

Cardirest is known to increase endocardial pacing thresholds, i.e. to decrease endocardial pacing sensitivity. This effect is reversible and is more marked on the acute pacing threshold than on the chronic. Cardirest should thus be used with caution in all patients with permanent pacemakers or temporary pacing electrodes, and not be administered to patients with existing poor thresholds or non-programmable pacemakers unless suitable pacing rescue is available.

Generally, threshold changes are within the range of multiprogrammable pacemakers and when these changes occur, usually a doubling of either voltage or pulse width is sufficient to regain capture. It may be difficult to obtain ventricular thresholds less than 1 volt at initial implantation in the presence of Cardirest.

The negative inotropic effect of Cardirest may be important in patients predisposed to cardiac failure. Difficulty has been experienced in defibrillating some patients. Most of the cases reported had pre-existing heart disease with cardiac enlargement, a history of myocardial infarction, arteriosclerotic heart disease and cardiac failure.

Pro-dysrhythmic Effects

Cardirest may cause pro-dysrhythmic effects. It may, for example, cause the appearance of a more severe type of dysrhythmia, increase the frequency of an existing dysrhythmia or increase the severity of the symptoms (see section 4.8).

Atrial fibrillation

Cardirest should be used with caution in patients with acute onset of atrial fibrillation following cardiac surgery.

Cardiac conduction

Cardirest prolongs the QT interval and widens the QRS complex by 12 - 20 %. The effect on the JT interval is insignificant.

Brugada syndrome

Brugada syndrome may be unmasked due to Cardirest therapy. In the case of development of ECG changes during treatment with Cardirest that may indicate Brugada syndrome, discontinuation of treatment is advised.

Bradycardia

Severe bradycardia or pronounced hypotension should be corrected before using Cardirest.

Electrolyte Disturbances

The presence of a potassium excess or deficit may alter the effects of Class I anti-dysrhythmic medicines. Any pre-existing hypokalaemia or hyperkalaemia or other electrolyte disturbances should be corrected before administration of Cardirest.

Switching to different formulation

Cardirest, as a narrow therapeutic index medicine, requires caution and close monitoring when switching a patient to a different formulation. Refer to section 4.5.

Use in hepatic impairment

Since flecainide elimination from the plasma can be markedly slower in patients with hepatic impairment, Cardirest should not be used in such patients unless the potential benefits clearly outweigh the risks. Plasma monitoring is strongly recommended in these circumstances.

Use in renal impairment

Cardirest should be used with caution in patients with impaired renal function (creatinine clearance ≤ 35 ml/min/1.73 m^2) and therapeutic monitoring is recommended.

Use in the elderly

The rate of flecainide elimination from plasma may be reduced in the elderly. This should be taken into consideration when making dose adjustments.

Paediatric population

Cardirest is not recommended in children under 18 years of age, as there is insufficient evidence of its use in this age group.

4.5 Interaction with other medicines and other forms of interaction

Use of Cardirest with other class 1 anti-dysrhythmics or calcium channel blockers with anti-dysrhythmic activity is not recommended.

Life-threatening or even lethal adverse events due to interactions causing increased plasma concentrations may occur (see section 4.9). Flecainide is metabolised by CYP2D6 to a large extent, and concurrent use of medicines inhibiting (e.g. antidepressants, neuroleptics, propranolol, ritonavir, some antihistamines) or inducing (e.g. phenytoin, phenobarbital, carbamazepine) this iso-enzyme can increase or decrease plasma concentrations of flecainide, respectively.

An increase of plasma levels may also result from renal impairment due to a reduced clearance of flecainide.

Anti-histamines

Avoid concomitant use with mizolastine and terfenadine it may increase the risk of ventricular dysrhythmias.

Antivirals

Plasma concentration of flecainide is increased by ritonavir, lopinavir and indinavir (increased risk of ventricular dysrhythmias); avoid concomitant use.

Diuretics

Class effect due to hypokalaemia giving rise to cardiac toxicity.

Hypokalaemia, but also hyperkalaemia or other electrolyte disturbances should be corrected before administration of flecainide. Hypokalaemia may result from the concomitant use of diuretics, corticosteroids or laxatives (see section 4.4).

Anti-depressants

Fluoxetine, paroxetine and other antidepressants increase plasma flecainide concentration; increased risk of dysrhythmias with tricyclics, caution is also advised with the concomitant administration of reboxetine.

Bupropion

Co-administration of bupropion with medicines that are metabolized by CYP2D6 isoenzyme including flecainide should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving flecainide, the need to decrease the dose of the original medication should be considered.

Cardiac glycosides

Cardirest can cause the plasma digoxin level to rise by about 15 %, which is unlikely to be of clinical significance for patients with plasma levels in the therapeutic range. It is recommended that the digoxin plasma level in digitalised patients should be measured not less than six hours after any digoxin dose, before or after administration of Cardirest.

Class II anti-dysrhythmics

The possibility of additive negative inotropic effects of beta-blockers and other cardiac depressants such as verapamil with flecainide should be considered.

Amiodarone

When Cardirest is given in the presence of amiodarone, the usual dose of Cardirest should be reduced by 50 % and the patient monitored closely for adverse effects. Plasma level monitoring is strongly recommended in these circumstances.

Cimetidine

Cimetidine inhibits metabolism of flecainide. In healthy subjects receiving cimetidine (1g daily) for one week, plasma flecainide levels increased by about 30% and the half-life increased by about 10 %.

Enzyme inducers

Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate a 30 % increase in the rate of flecainide elimination. In healthy subjects receiving cimetidine (1 g daily) for one week, plasma flecainide levels increased by about 30 % and the half-life increased by about 10 %. When amiodarone is added to Cardirest therapy, plasma flecainide levels may increase two-fold or more.

Therefore, the usual flecainide dosage should be reduced by at least 50 % and the patients monitored closely for adverse effects. Plasma level monitoring is strongly recommended in these circumstances.

Anti-malarial medicines

Quinine increases plasma concentration of flecainide.

Anti-psychotics

Concomitant use of Cardirest with clozapine may increase the risk of dysrhythmias.

Anticoagulants

Treatment with Cardirest is compatible with use of oral anti-coagulants.

4.6 Fertility, pregnancy and lactation

Pregnancy

Cardirest is contraindicated in pregnancy (see section 4.3).

Safety in pregnancy has not been established. Cardirest should not be administered in the case of suspected pregnancy or during the first three months of pregnancy.

Breastfeeding

Cardirest is contraindicated in breastfeeding women (see section 4.3).

Safety in breastfeeding has not been established.

4.7 Effects on ability to drive and use machines

Cardirest tablets have no or negligible influence on the ability to drive and use machines. However, driving ability, operation of machinery may be affected by adverse reactions such as dizziness and visual disturbances (if present).

4.8 Undesirable effects

System organ class	Frequency	
Blood and lymphatic system disorders	*Less frequent*	Decreased red blood cell count, white blood cell count and platelet count.
Immune system disorders	*Less frequent*	Antinuclear antibody increased with and without systemic inflammation.
Psychiatric disorders	*Less frequent*	Hallucination, depression, confusion, anxiety, amnesia and insomnia.
Nervous system disorders	*Frequent*	Giddiness, dizziness and light-headedness.
	Less frequent	Paraesthesia, ataxia, hypoaesthesia, hyperhidrosis, syncope, tremor, flushing, somnolence, headache, neuropathy peripheral, convulsion and dyskinesia.
Eye disorders	*Frequent*	Visual disturbances, such as diplopia and blurred vision.
	Less frequent	Corneal deposits.
Ear and labyrinth disorders	*Less frequent*	Tinnitus, vertigo.
Cardiac disorders	*Frequent*	Pro-dysrhythmic effects, occurs more frequently in patients with structural heart disease and/or significant left ventricular impairment (see section 4.4)[a].
	Less frequent	Patients with atrial flutter can develop a 1:1 AV conduction with increased heart rate.
	Frequency unknown	Dose-related increases in PR and QRS intervals may occur (see section 4.4). Altered pacing threshold (see section 4.4).
		Atrioventricular block second degree and atrioventricular block third degree, cardiac arrest, bradycardia, cardiac failure/cardiac failure congestive, chest pain, hypotension, myocardial infarction, palpitations, sinus pause or arrest, and tachycardia (AT or VT) or ventricular fibrillation. Demasking of a pre-existing Brugada syndrome.
Respiratory, thoracic and mediastinal disorders	*Frequent*	Dyspnoea.
	Less frequent	Pulmonary fibrosis, interstitial lung disease, pneumonitis.
Gastrointestinal disorders	*Less frequent*	Nausea, vomiting, constipation, abdominal pain, decreased appetite, diarrhoea, dyspepsia, flatulence.
Hepatobiliary disorders	*Less frequent*	Elevated hepatic enzymes with or without jaundice.
	Frequency unknown	Hepatic dysfunction.
Skin and subcutaneous	*Less frequent*	Allergic dermatitis, including rash, alopecia, serious urticaria

System organ class	Frequency	
tissue disorders		and photosensitivity reaction.
Musculoskeletal and connective tissue disorders	*Frequency unknown*	Arthralgia and myalgia.
General disorders and administration site conditions	*Frequent*	Asthenia, fatigue, pyrexia, oedema.

[a] In patients with atrial flutter the use of Cardirest has been associated with 1:1 AV conduction following initial arterial slowing with resultant ventricular acceleration. This has been seen frequently following the use of the injection for acute conversion. This effect is usually short lived and abates quickly following cessation of therapy. The rate of flecainide elimination from plasma may be reduced in elderly people and doses may need to be adjusted accordingly. The occurrence of cardiac arrest and symptomatic conduction disturbances is higher in the elderly.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Overdosage with Cardirest is a potentially life-threatening medical emergency.

Increased susceptibility and plasma levels exceeding therapeutic levels may also result from medicine interaction (see section 4.5). No specific antidote is known. There is no known way to rapidly remove flecainide from the system. Neither dialysis nor haemoperfusion is effective.

Treatment should be supportive and may include removal of unabsorbed medicine from the GI tract. Further measures may include inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol, as well as mechanical ventilation and circulatory assistance (e.g. balloon pumping). Temporarily inserting a transvenous pacemaker in the event of conduction block should be considered. Assuming a plasma half-life of approximately 20 h, these supportive treatments may need to be continued for an extended period of time. Forced diuresis with acidification of the urine theoretically promotes excretion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 6.2 Cardiac medicines.

Pharmacotherapeutic group: Class 1 anti-dysrhythmic (local anaesthetic) agent. ATC code: C01BC04.

Mechanism of Action

Flecainide is a class 1 anti-dysrhythmic (local anaesthetic) agent. Flecainide slows conduction through the heart, having its greatest effect on His bundle conduction. It also acts selectively to increase anterograde and particularly retrograde accessory pathway refractoriness.

Its action may be reflected in the ECG by prolongation of the PR interval and widening of the QRS complex. The effect on the JT interval is insignificant.

5.2 Pharmacokinetic properties

Absorption

Absorption of flecainide acetate via the oral route is greater than 80 % of the dose administered. After administration of one flecainide acetate tablet, plasma flecainide concentrations gradually increase after a lag time of 2 to 3 hours to reach a peak between the 21st and 25th hour and remain at plateau levels until after the 30th hour. Absorption of flecainide acetate is not modified by food.

Distribution

Steady-state is reached after five days of treatment with minimal fluctuations, and 50 % flattening of plasma concentration peaks compared to the tablet form. Flecainide acetate is widely and rapidly distributed in the tissues. The mean volume of distribution is 8,31 l/kg. Protein binding is low (about 40 %).

Elimination

Flecainide acetate is essentially eliminated in the urine:

25 % of the dose is eliminated after 24 hours in the unchanged form. Haemodialysis does not appear to be an effective way to eliminate flecainide acetate. Flecainide acetate is also eliminated by metabolism, especially via the cytochrome 2D6 pathway. The apparent plasma elimination half-life is about 12 to 14 hours; it is not modified with the flecainide acetate tablet form.

No enzyme induction or inhibition phenomena have been observed after prolonged dosing.

Linearity

Plasma concentrations are proportional to the dose between 50 mg and 300 mg. This dose relation is maintained at steady-state for doses of 100 to 300 mg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (Type 101)

Microcrystalline cellulose (Type 102)

Croscarmellose sodium

Pregelatinized starch

Hydrogenated vegetable oil (Type-1)

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

Aluminium/PVDC blister packs with 10 blister packs of 10 tablets each placed in an outer carton. Pack size of 100 tablets.

6.6 Special precautions for disposal and other handling

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8 REGISTRATION NUMBER

Cardirest 50 tablets: 56/6.5/0095

Cardirest 100 tablets: 56/6.5/0096

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 September 2023

10 DATE OF REVISION OF THE TEXT

11 July 2023