PROPOSED PROFESSIONAL INFORMATION TEMPACIN CR

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TEMPACIN 50 CR capsule

TEMPACIN 100 CR capsule

TEMPACIN 150 CR capsule

TEMPACIN 200 CR capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TEMPACIN CR is a hard gelatine capsule, filled with extended release mini film coated tablets, allowing controlled release of flecainide acetate.

Each **TEMPACIN CR** capsule contains either 50, 100, 150 or 200 mg flecainide acetate.

TEMPACIN CR is sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

TEMPACIN CR 50: Number 4 gelatine opaque capsules with white body and white cap containing white or almost white round micro-tablets.

TEMPACIN 100 CR: Number 3 gelatine opaque capsules with grey body and white cap containing white or almost white round micro-tablets.

TEMPACIN 150 CR: Number 2 gelatine opaque capsules with grey body and grey cap containing white or almost white round micro-tablets.

TEMPACIN 200 CR: Number 1 gelatine opaque capsules with grey body and pink cap containing white or almost white round micro-tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment with **TEMPACIN CR** should be initiated in a hospital for control of the following dysrhythmias:

- Sustained ventricular tachydysrhythmia.
- 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 will respond more readily.

TEMPACIN CR is indicated in premature ventricular contractions and/or non-sustained ventricular tachycardia which are causing disabling symptoms.

TEMPACIN CR can be used for the maintenance of normal rhythm following conversion by other means.

4.2 Posology and method of administration

Posology

Adults:

TEMPACIN CR is to be administered as a once daily dosage.

1. **Documented supraventricular tachycardia:**

The recommended starting dosage is 100 mg per day.

A dose increase should be considered only after a period of 4 to 5 days.

The optimal dose is 200 mg per day; the maximum dose is 300 mg per day.

2. Documented ventricular tachycardia:

The usual dosage is 200 mg per day

A dose increase should only be considered after a period of 4 to 5 days.

The maximum dosage is 300 mg per day.

3. High risk patients:

High risk patients include the elderly, patients with a history or symptoms suggestive of heart failure, severe renal insufficiency (creatinine less than or equal to 30 mL/min/m^2).

The initial dose must not exceed 100 mg per 24 hours. The dose ranges from 50 to 100 mg/24 hours depending on the patient's state.

The dosage of **TEMPACIN CR** can be increased or decreased by increments of 50 mg per day, bearing in mind that a minimum of 4 to 5 days is necessary to establish new steady-state plasma levels after each dosage change. Patients should be monitored by clinical examination and by electrocardiogram.

Note: If a patient is switched from a tablet formulation of flecainide acetate to **TEMPACIN CR**, the dose should be based on the total daily dose (e.g. 2 x 100 mg tablets to **TEMPACIN 200 CR**).

Method of administration

Oral.

PROPOSED PROFESSIONAL INFORMATION TEMPACIN CR

4.3 Contraindications

TEMPACIN CR must never be used in:

- Patients who are hypersensitive to flecainide acetate or to any of the inactive ingredients of **TEMPACIN CR** (see section 6.1)
- Myocardial infarction (old or acute).
- Heart failure, regardless of the type of dysrhythmia.
- Complete left bundle branch block, bi-fascicular block, 2nd and 3rd degree atrioventricular block, sinus node dysfunction and atrial disease, in the absence of pacing.
- Patients with long-standing atrial fibrillation and haemodynamically significant valvular heart disease.

TEMPACIN CR is generally not recommended in combination with class I antidysrhythmics.

4.4 Special warnings and precautions for use

Flecainide as in TEMPACIN CR was tested in a multicentre randomised double-blind trial (CAST trial) in patients with asymptomatic, non-life-threatening ventricular dysrhythmia with a history of myocardial infarction more than 6 days and less than 2 years before inclusion. The incidence of mortality and nonfatal cardiac arrests was higher with flecainide than in the placebo control group. No controlled trial has demonstrated a beneficial effect of flecainide as in TEMPACIN CR in terms of survival or sudden death.

TEMPACIN CR has a narrow therapeutic index and requires caution and close monitoring when switching a patient to a different formulation.

Electrocardiographic changes:

TEMPACIN CR must be administered cautiously in patients

with pre-existing conduction disorders.

TEMPACIN CR should be stopped if atrioventricular block, permanent complete branch block or sinoatrial block occur during treatment.

The dosage should be decreased in the case of widening of QRS complexes by more than 25 % of baseline values.

In the case of modification of the dosage of **TEMPACIN CR** or concomitant treatment able to affect cardiac conduction, patients, especially those with pre-existing conduction disorders, should be closely monitored by electrocardiogram.

Increases in endocardial pacing:

TEMPACIN CR is known to increase endocardial pacing thresholds i.e. to decrease endocardial pacing sensitivity. This effect is reversible and is clearer on the acute pacing threshold than on the chronic.

TEMPACIN CR should therefore be used with caution in all patients with permanent pacemakers or temporary pacing electrodes, and should not be administered to patients with existing poor thresholds or non-programmable pacemakers unless suitable pacing rescue is available.

Usually, a doubling of either pulse width or voltage is sufficient to regain capture, but it may be difficult to obtain ventricular thresholds less than 1 Volt at initial implantation in the presence of **TEMPACIN CR**.

History of heart failure:

TEMPACIN CR must be prescribed under strict surveillance of cardiac function in patients with a history or symptoms suggestive of heart failure, due to its negative inotropic properties.

Most of the cases reported had pre-existing heart disease with cardiac

enlargement, a history of myocardial infarction, arteriosclerotic heart disease and cardiac failure.

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

TEMPACIN CR should be avoided in patients with structural heart disease or abnormal left ventricular function.

Severe bradycardia or pronounced hypotension should be corrected before using **TEMPACIN CR**.

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

TEMPACIN CR prolongs the QT interval and widens the QRS complex by 12 – 20 %. The effect on the JT interval is insignificant.

A Brugada syndrome may be unmasked due to **TEMPACIN CR** therapy. In the case of development of electrocardiogram changes during treatment with **TEMPACIN CR** that may indicate Brugada syndrome, discontinuation of the treatment should be considered.

Pro-dysrhythmic effects:

TEMPACIN CR can induce a more severe form of dysrhythmia, increase the frequency of a pre-existing dysrhythmia or worsen the severity of symptoms (see section 4.8).

Spontaneous variations of the dysrhythmia specific to the patient may be difficult to distinguish from deterioration induced by administration of the medicine. Treatment of **TEMPACIN CR** should be stopped in the case of more numerous or polymorphous ventricular premature complexes.

Renal insufficiency, elderly:

TEMPACIN CR should be used with caution in patients with impaired renal function (creatinine clearance ≤ 35 mL/min/1,73 m^2) and therapeutic drug monitoring is recommended.

In patients with renal insufficiency and/or elderly subjects, the rate of elimination of **TEMPACIN CR** can be decreased, resulting in a risk of plasma and tissue accumulation of flecainide, which can be responsible for adverse effects. This risk justifies dosage adjustment.

Hepatic impairment:

Flecainide elimination from the plasma can be slower in patients with significant hepatic impairment, therefore **TEMPACIN CR** should be used with extreme caution in such patients. Monitoring of plasma levels is recommended.

Electrolyte disorders:

Hypokalaemia, hyperkalaemia or hypomagnesaemia can potentiate the pro-dysrhythmic effects of **TEMPACIN CR** and must therefore be corrected before the administration of **TEMPACIN CR**.

Elderly patients:

The rate of elimination from plasma may be reduced in the elderly and

doses of **TEMPACIN CR** may need to be adjusted accordingly. The occurrence of cardiac arrest and symptomatic conduction disturbances is higher in the elderly.

Paediatric population:

TEMPACIN CR 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

Class I antidysrhythmics:

TEMPACIN CR should not be administered concomitantly with other class I antidysrhythmics due to the risk of cardiac side effects (e.g. automatism, conduction, prodysrhythmic effects, inotropism).

Cardiac glycosides:

TEMPACIN CR may cause plasma digoxin levels to rise by about 15 %. It is recommended that digoxin plasma levels in digitalised patients are measured not less than 6 hours after any digoxin dose, before. or after taking **TEMPACIN CR**

Class II antidysrhythmics:

The possibility of additive negative inotropic effects of beta- blockers and other cardiac depressants with **TEMPACIN CR** should be recognised.

Class III antidysrhythmics:

If **TEMPACIN CR** is given in the presence of amiodarone the usual dosage of **TEMPACIN CR** should be reduced by 50 % and the patient monitored closely for adverse effects. Plasma level

monitoring is strongly recommended in these circumstances.

Class IV antidysrhythmics:

The use of **TEMPACIN CR** with other sodium channel blockers is not recommended.

Antidepressants:

Fluoxetine increases plasma levels of **TEMPACIN CR**, and there is an increased risk of dysrhythmias with tricyclics.

Inhibitors or inducers of isoenzyme CYP2D6:

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

Electrolyte disturbances:

Hypokalaemia but also hyperkalaemia or other electrolyte disturbances should be corrected before administration of **TEMPACIN CR**.
Hypokalaemia may result from the concomitant use of diuretics, corticosteroids or laxatives.

Antipsychotics:

Clozapine increases the risk of dysrhythmias.

Antimalarials:

Quinine increases the plasma concentration of **TEMPACIN CR**.

Antihistamines:

There is an increased risk of ventricular dysrhythmias with mizolastine and terfenadine, therefore concomitant use with **TEMPACIN CR** should be avoided.

Diuretics:

There is a class effect due to hypokalaemia giving rise to cardiotoxicity.

Cimetidine:

Co-administration with **TEMPACIN CR** results in an increase in plasma flecainide levels. Cimetidine inhibits metabolism of flecainide acetate. 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 %. Reduction of **TEMPACIN CR** dosage of up to 50 % is advisable.

Antismoking aids:

Co-administration of bupropion with **TEMPACIN CR** should be used with caution and should be initiated at the lower end of the dose range of the concomitant medicine. If bupropion is added to the treatment regimen of a patient already receiving **TEMPACIN CR**, the need to decrease the dose of **TEMPACIN CR** should be considered.

Anticoagulants:

The treatment with **TEMPACIN CR** is compatible with the use of oral anticoagulants.

An increase of plasma level may also result from renal impairment due to a reduced clearance of **TEMPACIN CR.**

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established. **TEMPACIN CR** should not be administered in the case of suspected pregnancy or during the first trimester of pregnancy.

Breastfeeding

Safety in breastfeeding has not been established.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines:

TEMPACIN CR may cause dizziness, visual disturbances and light-headedness. Caution is advised before driving a vehicle or operating machinery until the effects of **TEMPACIN CR** are known.

4.8 Undesirable effects

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Decreased red blood cell count, decreased white blood cell count, decreased platelet count
Immune system	Less frequent	Antinuclear antibody

disorders		increased, with and without systemic inflammation
Psychiatric disorders	Less frequent	Hallucination, depression, confusional state, anxiety, amnesia, insomnia
Nervous system disorders	Frequent Less frequent	Giddiness, dizziness, light-headedness (usually transient), peripheral neuropathy, paraesthesia, ataxia Hypoesthesia, hyperhidrosis, syncope, tremor, flushing, somnolence, headache, convulsions, seizure, dyskinesia
Eye disorders	Frequent Less frequent	Visual impairment, diplopia, blurred vision Corneal deposits
Ear and labyrinth disorders	Less frequent	Tinnitus, vertigo
Cardiac disorders	Frequent	Pro-dysrhythmic effects (most likely in patients with structural heart disease and/or significant left ventricular impairment), patients with atrial flutter can develop a 1:1 AV conduction with increased heart rate Dose-related increases in PR

	Frequency unknown	and QRS intervals, altered pacing threshold, atrioventricular block - second degree and atrioventricular block - third degree, cardiac arrest, bradycardia, cardiac failure / congestive cardiac failure, chest pain, hypotension, myocardial infarction, palpitations, sinus pause or arrest, tachycardia (AT or VT) or ventricular fibrillation. Demasking of a pre-existing Brugada syndrome
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Dyspnoea Interstitial lung disease or pneumonitis, pulmonary fibrosis
Gastrointestinal disorders	Less frequent	Nausea, vomiting, constipation, abdominal pain, decreased appetite, diarrhoea, dyspepsia, flatulence
Hepato-biliary disorders	Less frequent Frequency unknown	Increased hepatic enzymes, jaundice Hepatic dysfunction
Skin and subcutaneous tissue disorders	Less frequent	Photosensitivity, allergic dermatitis, including rash, alopecia, serious urticaria

Musculoskeletal, and connective tissue disorders	Frequency unknown	Arthralgia, myalgia
General disorders and administration site conditions	Frequent	Asthenia, fatigue, pyrexia, oedema

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare 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 **TEMPACIN CR** is a potentially life-threatening medical emergency. Increased medicine susceptibility and plasma levels exceeding therapeutic levels may also result from medicine interaction (see section 4.5).
Overdose with **TEMPACIN CR** requires monitoring in hospital in a specialised unit. Treatment is essentially symptomatic.
It is marked by electrocardiographic changes, particularly widening of the QRS complex and development of cardiogenic shock. It can be accompanied by neurosensory, neuropsychiatric and cardiac symptoms.

No specific antidote is known. There is also no known method of rapidly removing **TEMPACIN CR** from the system, but forced acid

diuresis may theoretically be helpful. Neither dialysis nor haemoperfusion is helpful and injections of anticholinergics are not recommended.

Treatment should be supportive and may include removal of unabsorbed medicine from the GI tract. Treatment may include therapy with an inotropic medicine, intravenous calcium, giving circulatory assistance (e.g. balloon pumping), mechanically assisting respiration or temporarily inserting a transvenous pacemaker if there are severe conduction disturbances, or the patient's left ventricular function is otherwise compromised. Assuming a plasma half-life of approximately 20 h, these supportive treatments may need to be continued for an extended period of time.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 6.2 Cardiac medicines (depressants) (Class I anti-dysrhythmic)

Pharmacotherapeutic group: Flecainide acetate is a Class 1 anti-arrhythmic (local anaesthetic) medicine. ATC code: C01BC04.

Flecainide acetate is a class I antidysrhythmic (local anaesthetic) medicine, which possesses a negative inotropic effect.

Flecainide acetate:

- prolongs intra-atrial, nodal and intraventricular conduction times
- slightly increases atrial and ventricular effective refractory periods
- increases the effective refractory period of the atrioventricular node
- increases the refractory period of retrograde and anterograde accessory pathways
- does not induce any significant modifications of heart rate except in patients with sinus node dysfunction.

There is a marked linear relationship between plasma flecainide acetate

concentrations and widening of the QRS complex, a marker of the antidysrhythmic effect.

5.2 Pharmacokinetic properties:

Absorption

Absorption of flecainide acetate via the oral route is greater than 80 % of the dose administered.

Absorption of flecainide acetate is not modified by food.

Distribution

After administration of one flecainide acetate capsule, plasma flecainide concentrations gradually increase after a lag time of 2 to 3 hours to reach a peak between 21 to 25 hours, and remain at plateau levels until after 30 hours.

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

Flecainide acetate is widely and rapidly distributed in the tissues. The mean volume of distribution is 8,31 L/kg with protein binding low (at 40 %).

Steady-state is reached after 5 days of treatment with minimal fluctuations, and 50 % flattening of plasma concentration peaks compared to the tablet formulation.

Biotransformation

No enzyme induction or inhibition have been reported after prolonged dosing.

Elimination

Flecainide acetate is eliminated in the urine, with 25 % of the dose eliminated after

24 hours in the unchanged form. Haemodialysis does not appear to eliminate flecainide acetate effectively.

Flecainide acetate is also eliminated by metabolism mainly via the cytochrome 2D6 pathway.

The plasma elimination half-life is about 12 to 14 hours; it is not modified with the flecainide acetate capsule form.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Extended release mini tablets:

Colloidal silicon dioxide

Crospovidone

Macrogol

Magnesium stearate

Methacrylic acid-methyl methacrylate copolymer

Microcrystalline cellulose

Polyvinyl pyrrolidone

Talc

Hard gelatine capsules:

TEMPACIN 50 CR: The capsule shell contains gelatine and titanium dioxide.

TEMPACIN 100 CR and **TEMPACIN 150 CR:** The capsule shell contains black iron oxide, gelatine and titanium dioxide.

TEMPACIN 200 CR: The capsule shell contains black iron oxide, red iron oxide, gelatine and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Transparent PVC/PVDC aluminium foil blister strips containing 6 or 10 capsules.

The blister strips are packed in an outer carton.

Pack size: 6, 10, 12, 30 or 60 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd.

Block B, Arena Office Park

272 West Avenue

Centurion

0157

South Africa

8. REGISTRATION NUMBERS

TEMPACIN 50 CR: 54/6.2/0421

TEMPACIN 100 CR: 54/6.2/0422

TEMPACIN 150 CR: 54/6.2/0423

TEMPACIN 200 CR: 54/6.2/0424

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 29 August 2023