Professional Information

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

TAMBOCOR 100 mg tablets

TAMBOCOR INJECTION 10 mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains flecainide acetate 100 mg.

Sugar free.

Each ampoule contains 15 ml of solution of flecainide acetate 10 mg/ml, for intravenous use only.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets: White, circular, biconvex tablets coded TR100 on one face with a break-line and plain on the other face.

Injection: A clear, colourless solution contained in a clear glass ampoule. The normal fill volume is 15,0 ml.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

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

a. Sustained ventricular dysrhythmias.

b. AV nodal reciprocating tachycardia; Wolff-Parkinson-White Syndrome and similar conditions with accessory pathway and anterograde or retrograde conduction.

c. Paroxysmal atrial fibrillation in patients with disabling symptoms. Dysrhythmias of recent onset are more likely to respond.

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

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

4.2 Posology and method of administration

a. Tablets:

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.

b. Bolus injection:

TAMBOCOR can be given in an emergency or for rapid effect by a slow intravenous injection of 2 mg/kg over not less than ten minutes, or in divided doses. If preferred, the dose may be diluted with 5 % dextrose and given as a mini-infusion.

Continuous ECG monitoring is recommended in all patients receiving the bolus dose. The injection should be stopped when control of the dysrhythmia has been achieved.

It is recommended that TAMBOCOR should be administered more slowly to patients in sustained ventricular tachycardia, with careful monitoring of the electrocardiogram. Similar caution should apply to patients with a history of cardiac failure, who may become decompensated during the administration. For such patients it is recommended that the initial dose be given over 30 minutes. The maximum recommended bolus dose is 150 mg.

c. Intravenous infusion:

When prolonged parenteral administration is required, it is recommended that therapy is initiated by slow injection of 2 mg/kg over 30 minutes and continued by intravenous infusion at the following rates:

First hour: 1,5 mg/kg per hour.

Second and later hours: 0,1 – 0,25 mg/kg per hour.

It is recommended that the infusion duration should not exceed 24 hours. However, where this is considered necessary, or for patients receiving the upper end of the dose range, plasma level monitoring is strongly recommended. The maximum cumulative dose given in the first 24 hours should not exceed 600 mg.

Transition to oral dosing should be accomplished as soon as possible by stopping the infusion and administering the first required oral dose.

Oral maintenance is then continued as indicated in the relevant oral dosage instructions.

Plasma levels: Based on 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.

Children: TAMBOCOR 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/1.73m2 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.

4.3 Contraindications

TAMBOCOR is contraindicated in:

- hypersensitivity to flecainide acetate or any of the excipients (see section 6.1)
- 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
- safety in pregnancy and lactation has not been established (see section 4.6).
- patients with long standing atrial fibrillation
- patients with haemodynamically significant valvular heart disease
- the presence of cardiogenic shock
- known Brugada syndrome

Unless pacing rescue is available, TAMBOCOR 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.

4.4 Special warnings and precautions for use

Electrolyte disturbances (e.g. hypo– and hyperkalaemia) should be corrected before using TAMBOCOR.

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

TAMBOCOR 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.

TAMBOCOR 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, a doubling of either pulse width or current 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 TAMBOCOR.

The negative inotropic effect of flecainide 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, arterio-sclerotic heart disease and cardiac failure.

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

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 to 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 TAMBOCOR favourably affects survival or the incidence of sudden death.

A Brugada syndrome may be unmasked due to flecainide therapy. In the case of development of ECG changes during treatment with flecainide that may indicate Brugada syndrome, consideration to discontinue the treatment should be made (see section 4.3).

As flecainide is a narrow therapeutic index medicine, caution and close monitoring is required when switching a patient to a different formulation.

Elderly patients:

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.

Hepato-biliary disorders:

Insufficient efficacy and safety data are available to recommend the use of TAMBOCOR in patients with liver function impairment.

Children:

TAMBOCOR 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

Flecainide is a Class I antidysrhythmic. The concomitant use with other Class I antidysrhythmic medicine is not recommended because of possible interactions where additive effects may occur.

The following medicines may interact with flecainide:

Cardiac glycosides:

Flecainide can cause the plasma digoxin level to rise by about 15 %. 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 flecainide.

Class II antidysrhythmics:

The possibility of additive negative effects of beta-blockers and other cardiac depressants with flecainide should be recognised.

Class III antidysrhythmics:

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

Class IV antidysrhythmics:

Use of flecainide with other calcium channel blockers is not recommended.

Antidepressants:

Fluoxetine, paroxetine and other antidepressants increases plasma flecainide concentration.

Increased risk of dysrhythmias with tricyclics.

Antiepileptics:

Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate a 30 % increase in the rate of flecainide elimination.

Antipsychotics:

Clozapine – increased risk of dysrhythmias.

Antihistamines:

Increased risk of ventricular dysrhythmias with mizolastine and terfenadine (avoid concomitant use).

Antimalarials:

Quinine increases plasma concentration of flecainide.

Antivirals:

Plasma concentration 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.

Antismoking aids:

Co-administration of bupropion with medicines that are metabolised 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 medicine. If bupropion is added to the treatment regimen of a patient already receiving flecainide, the need to decrease the dose of the original medicine should be considered.

H2-receptor blockers:

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 %.

Anticoagulants:

Treatment with TAMBOCOR is compatible with use of oral anticoagulants.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

No data available.

Pregnancy

Flecainide crosses the placenta. Safety in pregnancy has not been established. It should not be administrated in the case of suspected pregnancy or during the first three months of pregnancy.

Breastfeeding

Flecainide is distributed into breast milk. Safety in lactation has not been established and TAMBOCOR should not be administrated to mothers who are breastfeeding their infants.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

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

The effect of TAMBOCOR on the individual should always be known before they drive, operate machinery or work under hazardous conditions.

4.8 Undesirable effects

The following side effects have been observed during treatment with TAMBOCOR:

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000); frequency unknown (cannot be estimated from the available data).

Blood and lymphatic system disorders:

Uncommon: red blood cell count decreased, white blood cell count decreased and platelet count decreased.

Immune system disorders:

Very rare: antinuclear antibody increased with and without systemic inflammation.

Psychiatric disorders:

Rare: hallucinations, depression, confusion, anxiety, amnesia, insomnia.

Nervous system disorders:

Very common: Giddiness, dizziness, and light-headedness which are usually transient have been reported.

Rare: paraesthesia, ataxia, hypoaesthesia, hyperhidrosis, syncope, tremor, flushing, somnolence, headache, peripheral neuropathy, convulsions, dyskinesia.

Eye disorders:

Very common: Visual disturbances, such as double vision and blurred vision may occur.

Uncommon: Corneal deposits.

Ear and labyrinth disorders:

Rare: tinnitus, vertigo.

Cardiac disorders:

Common: Pro-dysrhythmic effects may occur in any patient but are very common in patients with structural heart disease and/or significant left ventricular impairment.

Uncommon: Patients with atrial flutter can develop a 1:1 AV conduction with increased heart.

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 or 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:

Common: dyspnoea.

Rare: pneumonitis.

Very rare: pulmonary fibrosis, interstitial lung disease.

Gastrointestinal disorders:

Uncommon: Nausea, vomiting, constipation, abdominal pain, decreased appetite, diarrhoea, dyspepsia, flatulence.

Hepato-biliary disorders:

Rare: Elevated liver enzymes and jaundice have been reported in association with TAMBOCOR treatment.

Skin and subcutaneous tissue disorders:

Uncommon: allergic dermatitis, including rash, alopecia

Rare: serious urticaria, photosensitivity.

Musculoskeletal and connective tissue disorders:

Unknown: Artralgia and Myalgia

General disorders and administration site conditions:

Common: asthenia, fatigue, pyrexia, oedema.

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: U30TUhttps://www.sahpra.org.za/Publications/Index/8publicationsU30T

Alternately you can contact iNova Pharmaceuticals (Pty) Ltd at +27 11 087 0000.

Website: www.inovapharma.co.za.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Overdosage with flecainide is a potentially life-threatening medical emergency. Increased medicine susceptibility and plasma levels exceeding therapeutic levels may also result from interaction with other medicines (see section 4.5).

No specific antidote is known. There is no known way of rapidly removing flecainide 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 may include therapy with an inotropic agent, 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 patients left ventricular function is otherwise compromised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 6.2 Cardiac depressants

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

Oral administration of flecainide results in extensive absorption, with bioavailability approaching 90 to 95 %. Flecainide does not appear to undergo significant hepatic first-pass metabolism. In patients, 200 to 500 mg flecainide daily produced plasma concentrations within

the therapeutic range of 200 – 1 000 µg/ℓ. Protein binding of flecainide is within the range 32 to 58 %.

Recovery of unchanged flecainide in urine of healthy subjects was approximately 42 % of 200 mg oral dose, whilst the two major metabolites (Meta-O-Dealkylated and Dealkylates Lactam Metabolites) accounted for a further 14 % each. The elimination half-life after oral administration was 12 to 27 hours.

Intravenous administration of 0,5 – 2,0 mg/kg to healthy subjects resulted in plasma concentrations ranging from 70 – 340 µg/ℓ. Protein binding ranges from 32 to 58 %. The mean volume of distribution in healthy subjects following intravenous infusion of 2 mg/kg was 512 litres.

The elimination half-life after IV administration to patients was 7 to 19 hours.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets:

- Croscarmellose sodium
- Hydrogenated vegetable oil
- Magnesium stearate
- Microcrystalline cellulose
- Pregelatinised maize starch

Injection:

- Glacial acetic acid
- Sodium acetate
- Water for injection

6.2 Incompatibilities

None known.

6.3 Shelf life

Tablets: 60 months.

Injection: 36 months.

6.4 Special precautions for storage

Tablets: Store in a cool, dry place at or below 30 °C.

Injection: Store at or below 30 °C. Protect from light.

Keep out of reach of children.

6.5 Nature and contents of container

Blister packs of 60 tablets.

Boxes containing 5 x 15 ml ampoules.

6.6 Special precautions for disposal

Tablets: No special requirements.

Injection: For single use only.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iNova Pharmaceuticals (Pty) Ltd.

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2007

8 REGISTRATION NUMBER

Tablets: S/6.2/17

Injection: S/6.2/16

9 DATE OF FIRST REGISTRATION

Tablets: 02 February 1995

Injection: 09 March 1994

10 DATE OF REVISION OF THE TEXT

20 September 2020