SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tambocor Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution for injection contains 10 mg flecainide acetate.
One ampoule containing 15 mL solution for injection contains 150 mg flecainide acetate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear, colourless solution for injection or infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Serious sustained life threatening ventricular arrhthymias that have not responded to other drugs.

4.2 Posology and method of administration

In an emergency or for rapid effect, or as a slow intravenous infusion when prolonged administration is required.
a) Bolus injection: Administer 2 mg/kg over not less than ten minutes, or in divided doses. Alternatively dilute with 5% dextrose and give as a mini-infusion.
Continuous ECG monitoring is recommended. Stop the injection when the arrhythmia is controlled.
For sustained ventricular tachycardia, or people with a history of cardiac failure (who may become decompensated during administration) give the initial dose over 30 minutes and monitor the ECG carefully.
The maximum recommended bolus dose is 150 mg.
b) Intravenous infusion: The recommended procedure is to start with a slow injection of 2 mg/kg over 30 minutes, then continue 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.
The maximum recommended infusion duration is 24 hours; if exceeded, and in patients receiving high doses, monitor plasma levels.
The maximum cumulative dose over the first 24 hours should not exceed 600 mg.
In severe renal impairment (creatinine clearance < 35 ml/min/1.73 sq.m.) reduce the above dosage recommendations by half.
Oral maintenance dosing should be started as soon as possible after stopping the infusion.

Children: Tambocor is not recommended in children under 12, as there is insufficient evidence of its use in this age group.

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

4.3 Contraindications

Patients with structural heart disease and/or impaired left ventricular function (manifest heart failure with a left ventricular ejection fraction of less than 35%) should not be treated with flecainide due to the increased risk of pro-arrhythmic effects. Flecainide is also contraindicated for use in:

- Hypersensitivity (allergy) to the active substance flecainide acetate or to any of the excipients listed in section 6.1
- After myocardial infarction, except in patients with life-threatening ventricular cardiac arrhythmias,
- Cardiogenic shock,
- Severe bradycardia,
- SA blocks,
- Second- or third-degree AV block and intra-atrial or intra-ventricular conduction defects and bundle branch block or distal block if no pacemaker is implanted,
- Sinus node dysfunction or tachy-brady syndrome if no pacemaker is implanted,
- Long-standing atrial fibrillation,
- Patients with haemodynamically significant heart valve defects,
- Concomitant use of class I antiarrhythmics,
- Known Brugada syndrome.

4.4 Special warnings and precautions for use

Intravenous use of flecainide should normally be carried out under ECG and blood pressure monitoring. It is advisable to ensure that equipment is available to provide any support needed during administration.

In particular in cases of severe heart, liver or kidney dysfunction where antiarrhythmic therapy with flecainide is necessary, or where patients are treated with concomitant flecainide and amiodarone or flecainide and cimetidine, any adjustment of the therapy, dose changes and long-term therapy shall be done by repeated ECG checks with simultaneous checks of the flecainide plasma level (see section 4.2).
Direct hospital or specialist supervision is also required for:

- Patients with AV nodal reciprocating tachycardia; arrhythmias associated with Wolff-Parkinson-White syndrome and similar conditions with accessory pathways
- Paroxysmal atrial fibrillation in patients with disabling symptoms

Electrolyte imbalances should be corrected before using flecainide. Hypokalaemia or hyperkalaemia can influence the effects of class I antiarrhythmics. Hypokalaemia may occur in patients taking concomitant diuretics, corticosteroids or laxatives.

Severe bradycardia or pronounced hypotension should be corrected with medications before using flecainide.

In case of pronounced cardiac output disturbance (heart failure NYHA class III-IV and/or LVEF less than 35%), treatment of life-threatening ventricular cardiac arrhythmias with flecainide should only occur once the heart failure is compensated through the use of additional medications to increase cardiac output.

Since flecainide elimination from the plasma may be significantly delayed in patients with significant hepatic and renal impairment (creatinine clearance less than 35 mL/min/1.73 m2), flecainide should not be used in these patients unless the potential benefits clearly outweigh the risks. Plasma level monitoring is strongly recommended for these patients.

Flecainide is known to increase the endocardial pacing threshold, i.e. it decreases endocardial pacing sensitivity. This effect is reversible and is more marked in acute pacing applications than in chronic ones.
Flecainide has a selective effect that increases the refractory period of anterograde and especially of retrograde conduction. In most patients, this presents on ECG as a widening of the QRS complex by 12–20% and prolongation of the QTc interval. Consequently, the effect on the JT interval is only slight. Nevertheless, there have been reports of prolongation of the JT interval of up to 4%. This action is less marked than that observed with the class Ia antiarrhythmic drugs.
Flecainide should thus be used with caution in all patients with permanent or temporary pacemakers, and should not be administered to patients with existing poorly managed thresholds or non-programmable pacemakers unless suitable pacing rescue is available to handle emergencies.

Generally, a doubling of either pulse width or voltage is sufficient to restore pacemaker function, but it may be difficult to obtain ventricular thresholds less than 1 volt at initial implantation in the presence of flecainide.

The minor negative inotropic effect of flecainide may assume importance in patients predisposed to cardiac failure. Difficulty has been experienced in defibrillating some patients, especially in those with pre-existing heart disease with cardiac enlargement, a history of myocardial infarction, arteriosclerotic cardiovascular disease and heart failure.
Flecainide, like other antiarrhythmics, may cause proarrhythmic effects, i.e. it may increase the severity or frequency of an existing arrhythmia (see section 4.8).
Flecainide should be avoided in patients with structural heart disease or abnormal left ventricular function (see section 4.8).
Flecainide should be used with caution in patients with acute onset of atrial fibrillation following cardiac surgery.
In a large-scale, placebo-controlled clinical trial, in post-myocardial infarction patients with asymptomatic arrhythmias, oral flecainide was associated with 2.2-fold higher incidence of mortality or non-fatal cardiac arrest as compared with a placebo. In that same study, an even higher mortality rate was observed in patients treated with flecainide who had more than one myocardial infarction.

Brugada syndrome may be unmasked by flecainide therapy. In the case of ECG changes that develop during treatment with flecainide that may indicate Brugada syndrome, consideration should be given to discontinuing the treatment.

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

Dairy products (milk, infant formula and possibly yoghurt) may reduce the absorption of flecainide in children and infants. Flecainide is not approved for use in children under 12 years of age; however, flecainide toxicity has been reported during treatment in children who reduced their intake of milk, and in infants who were switched from milk formula to dextrose-based products.

Since flecainide is a narrow therapeutic index drug, it requires caution and close monitoring when switching a patient to a different formulation.

Note:
During use, it is essential to consider that no evidence has yet been discovered for any class I antiarrhythmic that treating arrhythmias extends life.

Tambocor contains 37.6 mg sodium per ampoule, equivalent to 1.9% of the WHO recommended maximum daily sodium intake of 2 g in food.

4.5 Interaction with other medicinal products and other forms of interaction

It is important to consider the following interactions with this medicinal product:

Flecainide should not be administered concomitantly with other class I antiarrhythmics or other sodium channel blockers because of the increased risk of cardiac side effects (see section 4.3).
Flecainide and other class antiarrhythmics should only be administered concomitantly if there is a tangible therapeutic effect; this requires close clinical and ECG monitoring.

In view of the possible additive effects, due caution is required for the concomitant use of flecainide and drugs with a negative inotropic or bradycardic effect, as well as drugs that slow atrioventricular or intraventricular conduction, such as beta blockers, verapamil-type calcium antagonists, cardiac glycosides or amiodarone. These interactions require a dose reduction.
The concomitant use of flecainide and propranolol can increase the flecainide plasma level by up to 20% and the propranolol plasma level by up to 30%, which may make a dose adjustment necessary for both substances.
The concomitant use of flecainide and digoxin can increase the digoxin plasma level by about 15–25%. As such, digoxin effects should be monitored clinically by repeated ECG studies or digoxin plasma level studies as appropriate. It is recommended that the digoxin plasma level in digitalised patients be measured no less than 6 hours after any digoxin dose, before or after administration of flecainide.

Diuretics produce a class effect due to potential hypokalaemia giving rise to cardiotoxicity.

Treatment with flecainide is compatible with the concomitant use of oral anticoagulants.

Life-threatening or even lethal adverse events may occur due to interactions causing increased plasma concentrations (see section 4.9).
Concurrent use of flecainide and other drugs that are also metabolised by, or that inhibit, the cytochrome P450 2D6 (CYP2D6) can slow the breakdown and increase plasma concentrations of flecainide.

Inhibitors include, for example, antidepressants, neuroleptics, propranolol, ritonavir, some antihistamines; inducers include phenytoin, phenobarbital and carbamazepine.

<u>Enzyme inhibitors</u>
Antiarrhythmics
Concurrent use of flecainide and amiodarone can double the flecainide plasma level, meaning that the dose of flecainide should be reduced by up to 50% (see section 4.2).

Antihistamines
Increased risk of ventricular arrhythmias with concomitant use of mizolastine and terfenadine. Avoid concomitant use.
Concurrent use of flecainide and cimetidine can double the flecainide plasma level, especially in patients with reduced kidney function (renal failure), meaning that the dose of flecainide should be reduced by up to 50% (see section 4.2).

Antiviral substances
Concurrent use of flecainide and indinavir can increase the flecainide plasma level (increased risk of ventricular arrhythmias). Avoid concomitant use.

Antidepressants
Concurrent use of flecainide and fluoxetine, paroxetine or moclobemide can increase the flecainide plasma level. Concurrent use of flecainide and tricyclics increases the risk of arrhythmias.

Neuroleptics
Concurrent use of flecainide and clozapine increases the risk of arrhythmias.

Antimalarials
Quinine and quinidine increase the plasma concentration of flecainide.

Antifungals
Terbinafine may increase plasma concentrations of flecainide.

Co-administration of bupropion, a medication to help people stop smoking that is metabolised by CYP2D6, with flecainide should be approached with caution and should use the lowest effective dose 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 existing medication should be considered.

Enzyme inducers
Concurrent use of flecainide and known enzyme inducers (such as phenytoin, phenobarbital and carbamazepine) can increase the elimination of flecainide by up to 30%.

4.6 Fertility, pregnancy and lactation

There is no data, or insufficient data, regarding the use of flecainide in human pregnancy. Flecainide should only be used in pregnancy where there is a strictly defined indication, since flecainide crosses the placenta to the foetus.
Animal studies of a specific breed of rabbit have demonstrated reproductive toxicity.
Flecainide passes into human milk and appears in concentrations that reflect those in maternal blood. Flecainide should therefore not be used during breast-feeding.
There is no data on the influence of flecainide on human fertility. Animal studies have shown flecainide to have no influence on fertility.

4.7 Effects on ability to drive and use machines

The presence of visual disturbances (e.g. double vision) or effects on the central-nervous system (tiredness, dizziness) can impair responses to the extent that it reduces the ability to drive, operate machinery or work without a secure support. These effects are multiplied when the drug is combined with alcohol.

4.8 Undesirable effects

The most frequently reported undesirable effects are dizziness and visual disturbances, which occur in around 15% of patients. These effects usually disappear after a few days in the further course of the therapy, or can be resolved by reducing the dose.

The evaluation of undesirable effects is based on the following frequencies:

Very common:	≥ 1/10
Common:	≥ 1/100 to <1/10
Uncommon:	≥ 1/1 000 to <1/100
Rare:	≥ 1/10 000 to <1/1 000
Very rare:	<1/10 000
Not known:	(Frequency cannot be estimated from the available data)

Blood and lymphatic system disorders:
Uncommon: Leukocytopenia, thrombocytopenia, reduced red blood cell count. These changes are usually mild.

Immune system disorders:

Very rare:	Increase in anti-nuclear antibodies with or without systemic inflammation

Psychiatric disorders:

Common:	Depression, anxiety, insomnia
Uncommon:	Confusion, amnesia, hallucinations

Nervous system disorders:

Very common:	Dizziness (balance disorders), usually temporary
Common:	Headache, paraesthesia, hypoaesthesia, ataxia, syncope, flushing, increased sweating, tremor
Uncommon:	Dyskinesia, muscle twitching, peripheral neuropathy, cramps
Rare:	Drowsiness

Eye disorders:

Very common:	Vision disorders, e.g. double vision, colour halos around light sources, blurry vision
Very rare:	Corneal deposits

Diseases of the ear and labyrinth:

Common:	Tinnitus
Rare:	Vertigo

Cardiac disorders:

Common:	Proarrhythmic effects (most likely in patients with structural heart disease and/or significant left heart failure, see section 4.3 “Contraindications”). As a class I antiarrhythmic, flecainide may cause proarrhythmic effects, trigger new arrhythmias or change the frequency or severity of an existing arrhythmia. This can severely impair cardiac function, possibly resulting in cardiac arrest. Especially at higher doses of flecainide, there is the possibility of an increase in arrhythmias or heart rate. Both ventricular arrhythmias and ventricular tachycardia have been reported, e.g. an increase in ventricular extrasystoles, increased frequency of premature ventricular contractions, increased frequency and severity of ventricular tachycardia, ventricular fibrillation. Patients with atrial flutter receiving flecainide have developed 1:1 AV conduction after an initial slowing of atrial activity and subsequent acceleration of ventricular activity. Conduction disorders may worsen under treatment with flecainide. AV blocks (second- and third- degree), bundle branch block or SA block have been observed. Treatment with flecainide should be stopped in such cases. Bradycardia or sinus arrest can occur. Treatment with flecainide can cause heart failure. Previously undetected heart failure (latent heart failure, NYHA I) may worsen under treatment with flecainide (clinical manifestation). In this case, a dose reduction or compensation through co-administration of medications to increase cardiac output is required (see section 4.2).

Not known:	Cardiac arrest, chest pain, hypotension, myocardial infarction, palpitations, atrial tachycardia and unmasking of pre-existing Brugada syndrome can occur. Dose-dependent prolongation of the PR and QRS intervals and a change in pacing threshold can occur (see section 4.4).

Respiratory, thoracic and mediastinal disorders:

Common:	Respiratory distress
Uncommon:	Interstitial pneumonitis
Not known:	Pulmonary fibrosis, interstitial lung disease

Gastrointestinal disorders:

Common:	Nausea, vomiting, diarrhoea, digestive disturbance, constipation
Uncommon:	Dry mouth, taste disorders, abdominal pain, loss of appetite, flatulence

Hepatobiliary disorders:

Rare:	Elevated liver enzyme levels, with or without jaundice
Not known:	Hepatic dysfunction

Skin and subcutaneous tissue disorders:

Common:	Rash
Uncommon:	Allergic skin reactions, alopecia
Rare:	Severe urticaria
Very rare:	Photosensitivity

Musculoskeletal and connective tissue disorders:

Uncommon:	Arthralgia, myalgia (possibly with fever)

Reproductive system and breast disorders:

Uncommon:	Impotence

General disorders and administration site problems:

Common:	Weakness, fatigue, fever, oedema

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Overdose with flecainide is a potentially life-threatening medical emergency.
Increased drug susceptibility and plasma levels exceeding therapeutic levels may also result from drug interactions (see section 4.5).

The symptoms of flecainide overdose progress according to the intake dose, the time that detoxification measures are initiated, and the functional status of the myocardium.
Overdose can induce cardiac and extracardiac adverse effects; these are listed in section 4.8. Cases of severe intoxication, accidental or suicidal, may induce asystole, respiratory arrest and an acute increase in the endocardial stimulation threshold.

No specific antidote is known.

There is no known way to rapidly remove flecainide from the system; however, forced alkaline diuresis may theoretically be useful (for details of the pH-value-specific elimination of flecainide, see section 5.2).

The treatment should include the following:

General measures:
- Stop or reduce the dose of flecainide,
- Intensive medical measures to address the symptoms.

Measures to address SA block and AV block (second- or third- degree):
- Parasympatholytic therapy using atropine or ipratropium bromide. Sympathicotonic therapy using orciprenaline; possibly pacemaker therapy.

Measures to address intraventricular blocks (bundle branch block):
- Stop or reduce the dose of flecainide; possibly pacemaker therapy. If electrical stimulation with a pacemaker is unsuccessful, it is possible to use high doses of orciprenaline to try and improve myocardial function.

Measures to address acute cardiac decompensation, possibly with low blood pressure:

- Stop flecainide, rapid IV loading with cardiac glycosides; if there is existing pulmonary oedema, intravenous administration of furosemide, preload reduction through administration of high-dose nitrates, if required, catecholamines (e.g. adrenaline and/or dopamine/dobutamine and/or isoproterenol). Circulation support using an intra-aortic balloon pump can be attempted.

Specific measures in severe intoxication:
- For severe hypotension and bradycardia (usually in unconscious patients): Atropine 0.5–1 mg IV, adrenaline 0.5–1 mg IV, possibly adrenaline continuous drip infusion. The drip rate is based on the clinical effect; possibly parasympatholytic therapy with atropine/ipratropium bromide; possibly antibradycardia pacemaker stimulation.
- For cerebral seizures: e.g. diazepam IV, secure the airways, intubation if necessary and controlled ventilation under relaxation (e.g. pancuronium 2–6 mg).

For circulatory arrest due to asystole or ventricular fibrillation:
Basic measures for cardiopulmonary resuscitation (ABC rule):
- **A**irway: clear the airway or intubate.
- **B**reathing: provide rescue breathing, where possible with high-flow oxygen therapy.
- **C**irculation: i.e. external cardiac massage (if necessary for several hours!).

Adrenaline 0.5–1 mg IV or diluted with 10 mL isotonic sodium chloride solution via intratracheal tube if there is no central venous access near the heart. Depending on the clinical effect, the administration of adrenaline can be repeated several times.

- For ventricular fibrillation: Defibrillation. For refractory VF, 5–15 mval potassium chloride IV then repeat defibrillation.
- If it is not possible to induce conversion of malignant ventricular tachycardia using standard measures (see above), it is justifiable to attempt antitachycardia pacemaker stimulation (e.g. overdrive suppression).

- Balance the metabolic acidosis with sodium carbonate 8.4%, initially at 1 mL/kg BW IV; repeat after 15 minutes.

Intravenous administration of lipid emulsions or extracorporeal membrane oxygenation (ECMO) can be considered depending on the specific case
- Attempt to improve heart and kidney function through infusions with catecholamines added (e.g. adrenaline and/or dopamine/dobutamine).

- - Generally speaking for class I antiarrhythmics, conduction disorders caused by toxicity can be antagonistically affected through intravenous administration of concentrated sodium ion solution (approximately 100 mval sodium chloride solution IV). A serum sodium level of 145–150 mval/L should not be exceeded.

- - The administration of 25–100 mg dexamethasone or betamethasone IV and/or 40% mannitol or sorbitol solution, 1 mL/kg BW IV can be attempted for the purpose of cerebral oedema prophylaxis or therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: class Ic antiarrhythmic drug, ATC code: C01BC04

Flecainide acetate is a class Ic antiarrhythmic drug with negative inotropic effect. It binds to the sodium channels of the muscle membranes and results in a considerable decrease in cardiac excitation conduction speed and suppression of spontaneous premature ventricular complexes. In the myocardium, flecainide acetate binds heavily to fast sodium channels and thus slows the depolarisation speed; conduction in the atrium, AV node, ventricle and Purkinje fibres is reduced. The most pronounced effect is seen in the Purkinje fibres.

5.2 Pharmacokinetic properties

Distribution volume: 8.7 L/kg BW
pKa value: 9.3

In general, steady state conditions are reached after approximately 4 days (equivalent to approximately 5 half-lives). In patients with dose restrictions (see section 4.2), the altered flecainide metabolism and elimination rate can mean that it takes 6–8 days or in extreme cases even up to 20 days for steady state to be reached.

The average plasma half-life in patients with heart disease is around 20 hours. The vast majority of patients who were successfully treated with flecainide had plasma levels of 200–1 000 ng/mL, depending on the selected dose. In a period of 12 hours without administration of the drug, the flecainide plasma level decreases by 25–30%.
Flecainide does not experience any noteworthy first pass effect in the liver but does undergo significant secondary metabolism. The metabolites found to date show no or very little antiarrhythmic effect and according to current findings do not cause any adverse reactions. Flecainide and the metabolites found to date (including conjugated compounds) are almost completely eliminated through the kidneys; only 5% flecainide and metabolites were found in the faeces.

Investigations have found that flecainide elimination is dependent on urine pH. With a urine pH of 4.4–5.4, approximately 45% of a single flecainide dose is eliminated unchanged by the kidneys within 32 hours; with a urine pH of 7.4–8.3, the elimination rate of non-metabolised flecainide is 7.4%.
For interaction with other substances, see section 4.5.

The plasma protein binding of flecainide is 32–47% and is not affected by the dose administered or the flecainide plasma level. The free flecainide plasma level shows a close correlation with the dose administered.

5.3 Preclinical safety data

a) Acute toxicity
Acute toxicity of flecainide has been studied in mice, rats and dogs. The following LD_{50} values (half-maximum lethal doses) for flecainide were produced during a 14-day observation period:

	LD_{50} (mg/kg)		
	Oral	IV	IP
Mouse	190	24	79
Female rat	567	23	
Male rat	498	20	

In these studies on acute toxicity, there was observed ataxia, dyspnoea, convulsions and respiratory depression leading to death. In dogs, the lethal dose was 200 mg/kg after oral administration, and 20 mg/kg after IV injection.

b) Chronic toxicity
In dogs, flecainide caused changes in the ECG at doses over 5 mg/kg (prolonged PQ interval, severe widening of the QRS complex and the QT interval, increased T-wave amplitude, changes in heart rate, reduced contractility, conduction disorders). Flecainide induced elevated GPT in the blood (in rats from 80 mg/kg/day, in dogs from 5 mg/kg/day) and changes in the weight of the heart and liver, though without any histology changes observed in the heart and liver.

c) Mutagenic and tumorigenic potential
Mutagenicity tests carried out using flecainide (Ames test, mouse lymphoma assay, chromosome mutations in bone marrow in rats) provided no indication of a mutagenic effect.

Based on carcinogenicity studies (oral administration of flecainide at doses up to 60 mg/kg/day in mice for 18 months, in rats for 24 months) provided no indication of tumorigenic potential for flecainide.

d) Reproductive toxicity
Both teratogenicity and embryotoxicity have been demonstrated in one specific breed of rabbit. There is insufficient data available to determine a safety range for this effect. However, it has been confirmed that these effects have not occurred in other breeds of rabbits or in rats or mice.
Extended gestation periods have been observed in rats at a daily dose of 50 mg/kg or more. There were no effects on fertility.

There is insufficient experience in humans with use during pregnancy and lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium acetate , Glacial Acetic acid, , water for injection

6.2 Incompatibilities

When necessary, Tambocor injection should be diluted with, or injected into, sterile solutions of 5% glucose. If chloride containing solutions, such as sodium chloride or Ringer's lactate are used, the injection should be added to a volume of not less than 500 ml, otherwise a precipitate will form.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

Chemical and physical in-use stability of the diluted solutions have been demonstrated for 24 hours at room temperature.
From a microbiological point of view, the product should be used immediately.
If not used immediately, in-use storage times and conditions would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze. Protect from light, and keep the ampules in the outer carton.

6.5 Nature and contents of container

Boxes containing 5 x 15 ml ampoules glass TYPE I.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER

CENEXI , 52 RUE MARCEL ET JACQUES GAUCHER, 94120 FONTENAY-SOUS-BOIS, FRANCE

8. License Holder:

MEGAPHARM LTD.
POB 519, HOD HASHARON 4510501

9. MARKETING AUTHORISATION NUMBER(S)

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