APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. Name of the medicine

ADENOSINE 3 mg/1 ml PS FRESENIUS solution for injection

ADENOSINE 6 mg/2 ml PS FRESENIUS solution for injection

ADENOSINE 12 mg/4 ml PS FRESENIUS solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prefilled syringe contains 3 mg of adenosine per ml.

The solution is filled into syringes of the below given container size:

- 3 mg in 1 mL in 1 mL syringe
- 6 mg in 2 mL in 5 mL syringe
- 12 mg in 4 mL in 5 mL syringe

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear, colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Conversion to sinus rhythm of paroxysmal supraventricular tachycardia, including those associated with accessory by-pass tracts (Wolff-Parkinson-White syndrome).

4.2 Posology and method of administration

ADENOSINE PS FRESENIUS should only be used when facilities exist for cardiac monitoring and resuscitation.

Posology

Adults:

Initial dose: 3 mg given as a rapid intravenous bolus (over 2 seconds).

Second dose: If the first dose does not result in elimination of the supraventricular tachycardia within 1 to 2 minutes, 6 mg should be given also as a rapid intravenous bolus.

Third dose: If the second dose does not result in elimination of the supraventricular tachycardia within 1 to 2 minutes, 12 mg should be given also as a rapid intravenous bolus.

Patients who develop high-level atrioventricular (AV) block at a particular dose should not be given further dosage increments.

Additional or higher doses are not recommended.

Children:

No controlled paediatric study has been undertaken.

Elderly:

Dosage is as for adults.

Method of administration

ADENOSINE PS FRESENIUS should be administered by rapid intravenous (IV) bolus injection.

To be certain the solution reaches the systemic circulation, administer either directly into a vein or into an IV line. If given into an IV line, it should be injected as proximally as possible, and followed by a rapid saline flush.

For handling instructions of the prefilled syringe, refer to section 6.6

4.3 Contraindications

ADENOSINE PS FRESENIUS is contraindicated for patients with:

- Hypersensitivity to adenosine or to any of the excipients of ADENOSINE PS FRESENIUS listed in section 6.1.
- Second or third degree AV block (except in patients with a functioning artificial pacemaker).
- Sick sinus syndrome (except in patients with a functioning artificial pacemaker).
- Asthma.
- Long QT syndrome.
- Severe hypotension
- Decompensated states of heart failure.

4.4 Special warnings and precautions for use

Cardiac effects

Due to the possibility of transient cardiac dysrhythmias arising during conversion of the supraventricular tachycardia to normal sinus rhythm, administration should be carried out in a hospital setting with monitoring and cardio-respiratory resuscitation equipment available for immediate use if necessary. During administration, continuous ECG monitoring is necessary as life-threatening dysrhythmia might occur (see section 4.2).

Because it has the potential to cause significant hypotension, ADENOSINE PS FRESENIUS should be used with caution in patients with left main coronary stenosis, uncorrected hypovolaemia, stenotic valvular heart disease, left to right shunt, pericarditis or pericardial effusion, autonomic dysfunction or stenotic carotid artery disease with cerebrovascular insufficiency. There have been reports of cerebrovascular accident/transient ischemic attack, secondary to the haemodynamic effects of ADENOSINE PS FRESENIUS.

The occurrence of angina, severe bradycardia, severe hypotension, respiratory failure (potentially fatal), or asystole/cardiac arrest (potentially fatal), should lead to immediate discontinuation of administration.

There have been reports of myocardial infarction shortly after use of ADENOSINE PS FRESENIUS. ADENOSINE PS FRESENIUS should be used with caution in patients with recent myocardial

infarction, severe heart failure, or in patients with minor conduction defects (first degree A-V block, bundle branch block) that could be transiently aggravated during infusion.

ADENOSINE PS FRESENIUS should be used with caution in patients with atrial fibrillation or flutter and especially in those with an accessory by-pass tract since particularly the latter may develop increased conduction down the anomalous pathway.

Cases of severe bradycardia have been reported. Some occurred in early post heart transplant patients; in the other cases, occult sinoatrial disease was present. The occurrence of severe bradycardia should be taken as a warning of underlying disease and could potentially favour the occurrence of torsades de pointes, especially in patients with prolonged QT intervals.

Because of the possible risk of torsades de pointes, ADENOSINE PS FRESENIUS should be used with caution in patients with a prolonged QT interval, whether this is medicine induced or of metabolic origin. ADENOSINE PS FRESENIUS is contraindicated in patients with long QT syndrome (see section 4.3).

In patients with recent heart transplantation (less than 1 year) an increased sensitivity of the heart to adenosine (contained in ADENOSINE PS FRESENIUS) has been observed.

Renal and hepatic dysfunction

Since neither the kidney nor the liver are involved in the degradation of exogenous adenosine, the efficacy of ADENOSINE PS FRESENIUS should be unaffected by hepatic or renal insufficiency.

Dipyridamole

As dipyridamole is a known inhibitor of adenosine uptake, it may potentiate the action of adenosine. It is therefore suggested that ADENOSINE PS FRESENIUS should not be administered to patients receiving dipyridamole. If use of ADENOSINE PS FRESENIUS is essential, dipyridamole should be stopped 24 hours beforehand, or the dose of ADENOSINE PS FRESENIUS should be greatly reduced (see section 4.5).

Convulsions

Adenosine may trigger convulsions in patients who are susceptible to convulsions. In patients with history of convulsions/seizures, the administration of ADENOSINE PS FRESENIUS should be carefully monitored.

Bronchospasm

Adenosine may precipitate or aggravate bronchospasm (see sections 4.3 and 4.8).

Information on the excipients

ADENOSINE PS FRESENIUS contains 9 mg sodium chloride per ml (corresponding to 3,54 mg sodium per ml). To be taken into consideration by patients on a controlled sodium diet.

Paediatric population

No controlled paediatric study has been done.

4.5 Interaction with other medicines and other forms of interaction

Dipyridamole inhibits adenosine cellular uptake and metabolism and potentiates the action of adenosine. In one study dipyridamole was shown to produce a 4-fold increase in adenosine actions. Asystole has been reported following concomitant administration. It is therefore suggested that ADENOSINE PS FRESENIUS should not be administered to patients receiving dipyridamole; if use of ADENOSINE PS FRESENIUS is essential, dipyridamole should be stopped 24 hours beforehand, or the dose of ADENOSINE PS FRESENIUS should be greatly reduced (see section 4.4).

Aminophylline, theophylline and other xanthines such as caffeine are competitive adenosine antagonists and should be avoided for 24 hours prior to use of adenosine.

ADENOSINE PS FRESENIUS may interact with medicines tending to impair cardiac conduction.

Carbamazepine has been reported to increase the degree of heart block produced by other medicines. As the primary effect of adenosine is to decrease conduction through the AV node, higher degrees of heart block may be produced in the presence of carbamazepine.

Food and drinks containing xanthines (tea, coffee, chocolate, and cola) should be avoided for at least 12 hours prior to use of ADENOSINE FRESENIUS PS.

4.6 Fertility, pregnancy and lactation

Pregnancy

In the absence of evidence that adenosine does not cause foetal harm, ADENOSINE PS FRESENIUS should only be used during pregnancy where absolutely necessary.

Breastfeeding

In the absence of clinical experience, use of ADENOSINE PS FRESENIUS during breastfeeding should be considered only if essential.

Fertility

No data is available.

4.7 Effects on ability to drive and use machines

ADENOSINE PS FRESENIUS can cause dizziness, hypotension and lightheadedness. Patients should be advised not to drive or operate machines until they know how ADENOSINE PS FRESENIUS affects them.

4.8 Undesirable effects

Summary of the safety profile

The side effects are generally mild, of short duration (usually less than 1 minute) and well tolerated by the patient. However severe reactions can occur.

Methylxanthines, such as IV aminophylline or theophylline have been used to terminate persistent side effects (50 – 125 mg by slow intravenous injection).

Tabulated list of adverse events

Immune system disorders:

Frequency unknown:	anaphylactic reaction (including angioedema and skin reactions such as urticaria and rash)
Cardiac disorders:	
Frequent:	bradycardia, sinus pause, skipped beats, atrial extrasystoles, AV block, ventricular excitability disorders such as ventricular extrasystoles, non-sustained ventricular tachycardia
Less frequent:	sinus tachycardia, palpitations, atrial fibrillation, severe bradycardia not corrected by atropine and possibly requiring temporary pacing, ventricular excitability disorders, including ventricular fibrillation and torsade de pointes (see section 4.4)
Frequency unknown:	asystole/cardiac arrest, sometimes fatal especially in patients with underlying ischemic heart disease/cardiac disorder (see section 4.4)
Vascular disorders:	
Frequent:	flushing
Frequency unknown:	hypotension (sometimes severe) (see section 4.4)
Psychiatric disorders:	
Frequent:	apprehension, nervousness
Nervous system disorders:	
Frequent:	headache, dizziness, light-headedness, paraesthesia
Less frequent:	head pressure, transient and spontaneously rapidly reversible worsening of intracranial hypertension
Frequency unknown:	loss of consciousness/syncope, convulsions, especially in predisposed patients (see section 4.4)
Eye disorders:	
Less frequent:	blurred vision
Respiratory, thoracic, and mediastinal disorders:	
Frequent:	dyspnoea (or the urge to take a deep breath)

Less frequent:	hyperventilation, bronchospasm (see section 4.4)
Frequency unknown:	respiratory failure (see section 4.4), apnoea/respiratory arrest, cases of respiratory failure, bronchospasm, apnoea, and respiratory arrest with fatal outcome have been reported.
Gastrointestinal disorders:	
Frequent:	nausea
Less frequent:	metallic taste
Frequency unknown:	vomiting
General disorders and administration site conditions:	
Frequent:	chest pain or pressure, feeling of thoracic constriction/oppression
Less frequent:	sweating, discomfort in the leg, arm or back, feeling of general discomfort, weakness/pain, injection site reactions.

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

No cases of overdosage have been reported. Overdose would cause severe hypotension, bradycardia or asystole. As the half-life of adenosine in blood is very short, the duration of any side effects due to overdose is expected to be limited.

IV aminophylline or theophylline may be needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 6.2 Cardiac depressants

Pharmacotherapeutic group: Other Cardiac Preparations: ATC Code: C01EB 10

ADENOSINE PS FRESENIUS (adenosine) administered by rapid intravenous injection slows conduction through the AV node. This action can interrupt re-entry circuits involving the AV node and restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardias. Once the circuit has been interrupted, the tachycardia stops and normal sinus rhythm is re-established.

5.2 Pharmacokinetic properties

Neither the kidney nor the liver is involved in the degradation of exogenous adenosine.

An efficient salvage and recycling system exists in the body, primarily in

the erythrocytes and blood vessel endothelial cells. The half-life in vitro is estimated to be< 10 seconds.

The in vivo half-life may be even shorter.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injection

6.2 Incompatibilities

Compatibility with other medicines is not known.

6.3 Shelf life

36 months.

Any portion of the vial not used at once should be discarded.

6.4 Special precautions for storage

Store at or below 25 °C. Do not refrigerate.

6.5 Nature and contents of container

Cyclic olefin copolymer (COC) syringes, with a grey halobutyl plunger and closed with a Luer Lock tip cap and halobutyl stopper:

- 1 mL size single-use prefilled syringe containing 3 mg adenosine/mL solution. Available in cartons containing 10 individually boxed syringes
- 5 mL size single-use prefilled syringe containing 6 mg adenosine/2 mL solution (3 mg/mL). Available in cartons containing 10 individually boxed syringes
- 5 mL size single-use prefilled syringe containing 12 mg adenosine/4 mL solution (3 mg/mL). Available in cartons containing 10 individually boxed syringes

Vial stoppers and syringe stoppers do not contain natural rubber latex.

Not all packing sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

The new TopPac® syringe delivery system easily adapts to most peripheral line connection valves without the use of a needle. A needle is not provided with the Adenosine Injection TopPac® syringe delivery system. Should you require the use of a needle to inject ADENOSINE PS FRESENIUS directly into a vein, the adaptable Luer Lock tip can accommodate an 18 or 20 gauge needle.

To use the syringe, remove Luer cover.

Hold plunger and push barrel forward to relieve any resistance that may be present. Pull the barrel down until air is expelled from the syringe.

ADENOSINE PS FRESENIUS Injection is now ready to be administered (see section 4.2).

Syringes are intended for single-use only.

Handling instructions

To prevent needle stick injuries needles should not be recapped, purposely bent, or broken by hand. TopPac® is a latex free, plastic delivery system and is a registered trademark of Schott. Any portion of the syringe not used at once should be discarded.

7 HOLDER OF CERTIFICATES OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House, Midrand 1685

South Africa

8 REGISTRATION NUMBER(S)

ADENOSINE 3 mg/1 ml PS FRESENIUS: 50/6.2/0391

ADENOSINE 6 mg/2 ml PS FRESENIUS: 50/6.2/0392

ADENOSINE 12 mg/4 ml PS FRESENIUS: 50/6.2/0393

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 February 2021

10 DATE OF REVISION OF THE TEXT

02 February 2021