1 PRODUCT NAME

ADENOSINE BAXTER 30mg/10mL solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

ADENOSINE BAXTER solution for infusion vials contain 30mg in 10mL adenosine (equivalent to 3mg/mL).

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless to almost colourless solution essentially free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous **ADENOSINE BAXTER** 30mg/10mL is a coronary vasodilator for use in conjunction with radionuclide myocardial perfusion imaging, in patients unable to exercise adequately.

4.2 Dose and method of administration

ADENOSINE BAXTER 30mg/10mL is intended for use in hospitals, where facilities for cardiac monitoring and resuscitation are available.

Diagnostic dose

Adults

1. **ADENOSINE BAXTER** 30mg/10mL should be administered undiluted as a continuous peripheral intravenous infusion at a dose of 140µg/kg/min over fixed time interval of six minutes (total dose 0.84mg/kg) using an infusion pump. Separate venous sites for **ADENOSINE BAXTER** 30mg/10mL and radionuclide administration are recommended to avoid an adenosine bolus effect.
2. After three minutes of **ADENOSINE BAXTER** 30mg/10mL infusion, the radionuclide is injected.
3. Heart rate and blood pressure should be recorded at 1-minute intervals, and ECG should be monitored continuously during **ADENOSINE BAXTER** 30mg/10mL infusion. To avoid an adenosine bolus effect, blood pressure should be measured in the arm opposite to the **ADENOSINE BAXTER** 30mg/10mL infusion.

The table below is given as a guide for adjustment of the infusion rate of undiluted **ADENOSINE BAXTER** 30mg/10mL, in line with body weight (total dose 0.84mg/kg).

Patient weight (kg)	Infusion rate (mL/min)
45-49	2.1
50-54	2.3
55-59	2.6
60-64	2.8
65-69	3.0
70-74	3.3
75-79	3.5
80-84	3.8
85-89	4.0
90-94	4.2
95-99	4.4
100-104	4.7

Children

In the absence of data, the use of **ADENOSINE BAXTER** 30mg/10mL in children cannot be recommended.

Elderly

See dosage recommendations for adults.

4.3 Contraindications

ADENOSINE BAXTER 30mg/10mL is contraindicated for patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Sick sinus syndrome, second or third degree AV block (except in patients with a functioning artificial pacemaker)
- Chronic obstructive lung disease (such as asthma)
- Long QT syndrome
- Severe hypotension, decompensated states of heart failure
- Unstable angina not successfully stabilised with medical therapy
- Concomitant use of dipyridamole (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

ADENOSINE BAXTER 30mg/10mL is intended for use by physicians familiar with the product (see section 4.2) in a hospital setting with monitoring and cardio-respiratory resuscitation equipment available for immediate use if necessary.

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.

In patients with history of convulsions/seizures, the administration of adenosine should be carefully monitored.

As dipyridamole is a known inhibitor of adenosine uptake, it may potentiate the action of adenosine administration. The use of **ADENOSINE BAXTER** 30mg/10mL infusion is contraindicated in patients receiving dipyridamole (see section 4.3). If use of adenosine bolus injection (**ADENOSINE BAXTER** 6mg/2mL) is judged to be essential, dipyridamole should be discontinued 24 hours beforehand, or the dose of adenosine should be significantly reduced.

Myocardial infarction and life threatening ventricular arrythmias

Non-fatal myocardial infarction and sustained ventricular tachycardia (requiring resuscitation) have been reported coincident with adenosine. **ADENOSINE BAXTER** 30mg/10mL should be used with caution in patients with unstable angina or recent myocardial infarction.

Post heart transplantation

In patients with recent heart transplantation (less than 1 year) an increased sensitivity of the heart to adenosine has been observed. **ADENOSINE BAXTER** 30mg/10mL should be used with caution in such cases.

Sinoatrial and atrioventricular nodal block

Adenosine exerts a direct depressant effect on the SA and AV nodes and has the potential to cause first-, second-, or third-degree AV block, or sinus bradycardia. Approximately 6.3% of patients develop AV block with adenosine, including first-degree (2.9%), second-degree (2.6%) and third-degree (0.8%) heart block. All episodes of AV block have been asymptomatic, transient, and did not require intervention.

ADENOSINE BAXTER 30mg/10mL should be used with caution in patients with heart failure, or in patients with minor conduction defects (first degree AV block, bundle branch block) that could be transiently aggravated during infusion. **ADENOSINE BAXTER** 30mg/10mL should also be avoided in patients with high-grade AV block or sinus node dysfunction (except in patients with a functioning artificial pacemaker). **ADENOSINE BAXTER** 30mg/10mL should be discontinued in any patient who develops persistent or symptomatic high-grade AV block. If first-degree AV block occurs, the patient should be carefully observed for progression to a higher degree of block. Sinus pause has been rarely observed with adenosine infusions.

Bradycardia

Some cases of severe bradycardia have been reported. Some occurred in early post heart transplant patients; in other cases, occult sino-atrial 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.

Atrial fibrillation

ADENOSINE BAXTER 30mg/10mL should be used with caution in patients with atrial fibrillation or flutter and especially those with an accessory pathway since particularly the latter may develop increased conduction down the anomalous pathway.

Hypotension

Adenosine is a potent peripheral vasodilator and can cause significant hypotension. Patients with an intact baroreceptor reflex mechanism are able to maintain blood pressure and tissue perfusion in response to adenosine by increasing heart rate and cardiac output. However, **ADENOSINE BAXTER** 30mg/10mL should be used with caution in patients with autonomic dysfunction, stenotic valvular heart disease, left to right shunt, left main coronary artery stenosis, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, severe heart failure or uncorrected hypovolaemia, due to the risk of hypotensive complications in these patients.

ADENOSINE BAXTER 30mg/10mL should be discontinued in any patient who develops persistent or symptomatic hypotension.

Hypertension

Increases in systolic and diastolic pressure have been observed (as great as 140mmHg systolic in one case) concomitant with adenosine infusion: most increases resolved spontaneously within several minutes, but in some cases, hypertension lasted for several hours.

Bronchoconstriction

Adenosine is a respiratory stimulant (probably through activation of carotid body chemoreceptors) and intravenous administration in man has been shown to increase minute ventilation (V_E) and reduce arterial PCO_2 causing respiratory alkalosis. Approximately 28% of patients experience breathlessness (dyspnoea) or an urge to breathe deeply with adenosine. These respiratory complaints are transient and only rarely require intervention.

Adenosine administered by inhalation has been reported to cause bronchoconstriction in asthmatic patients, presumably due to mast cell degranulation and histamine release. These effects have not been observed in normal subjects. Adenosine has been administered to a limited number of patients with asthma and mild to moderate exacerbation of their symptoms has been reported.

Respiratory compromise has occurred during adenosine infusion in patients with obstructive pulmonary disease. **ADENOSINE BAXTER** 30mg/10mL should be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (e.g. emphysema, bronchitis, etc.) and should be avoided in patients with bronchoconstriction or bronchospasm (e.g. asthma). **ADENOSINE BAXTER** 30mg/10mL should be discontinued in any patient who develops severe respiratory difficulties.

Adenosine may precipitate or aggravate bronchospasm.

Use in hepatic impairment

For further information see Section 5.2.

Use in renal impairment

For further information see Section 5.2.

Use in the elderly

No data available.

Paediatric use

The safety and effectiveness of adenosine in patients less than 18 years of age have not been established.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

Adenosine has been safely and effectively administered in the presence of other cardioactive drugs such as digitalis, beta adrenergic blocking agents, and calcium channel antagonists. Because of the potential for additive or synergistic depressant effects of the SA and AV nodes, however, **ADENOSINE BAXTER** 30mg/10mL should be used with caution in the presence of these agents.

Adenosine may interact with drugs that tend to impair cardiac conduction.

Aminophylline, theophylline and other xanthines are competitive adenosine antagonists and should be avoided for 24 hours prior to the administration of **ADENOSINE BAXTER** 30mg/10mL.

Food and drinks containing xanthines (e.g. coffee, tea, chocolate and cola) should be avoided for at least 12 hours prior to the administration of adenosine. Nucleoside transport inhibitors such as dipyridamole inhibit adenosine cellular uptake and metabolism, and potentiate the action of adenosine. In one study, dipyridamole was shown to produce a four-fold increase in adenosine activity.

The use of **ADENOSINE BAXTER** 30mg/10mL infusion is contraindicated in patients receiving dipyridamole (see section 4.3). If the use of adenosine bolus injection (**ADENOSINE BAXTER** 6mg/2mL) is judged to be essential, dipyridamole should be discontinued 24 hours beforehand or the dose of adenosine should be significantly reduced.

Whenever possible, medicines that might inhibit or augment the effects of adenosine should be withheld for at least five half-lives prior to the use of **ADENOSINE BAXTER** 30mg/10mL.

4.6 Fertility, pregnancy and lactation

Fertility

In rats and mice, adenosine administered IP once a day for 5 days at 50, 100 and 150mg/kg caused decreased spermatogenesis and increased numbers of abnormal sperm.

Use in pregnancy (Category B2)

Animal reproductive studies have not been conducted with adenosine, nor have studies been performed on pregnant women. In the absence of evidence that adenosine does not cause foetal harm, **ADENOSINE BAXTER** 30mg/10mL should not be used during pregnancy unless the physician considers the benefits outweigh the potential risks.

Breast-feeding

Studies have not been performed in lactating animals or women. Therefore, **ADENOSINE BAXTER** 30mg/10mL should not be used during lactation. If **ADENOSINE BAXTER** 30mg/10mL treatment is considered essential by the physician, another form of infant feeding should be considered.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

The following reactions with an incidence of at least 1% were reported with adenosine continuous intravenous infusion among 1421 patients enrolled in controlled and uncontrolled U.S. clinical trials. Despite the short half-life of adenosine, 10.6% of the side effects occurred not with the infusion of adenosine but several hours after the infusion terminated. Also, 8.4% of the side effects that began coincident with the infusion persisted for up to 24 hours after the infusion was complete. In many cases, it is not possible to know whether these late adverse events are the result of adenosine infusion.

These adverse reactions have been classified using standard terminology and are categorised by body system. They are listed in order of decreasing frequency according to the following definitions:

Very common:	≥ 1/10 (10%)
Common:	≥ 1/100 (1%) and < 1/10 (10%)
Uncommon:	≥ 1/1000 (0.1%) and < 1/100 (1%)
Rare:	≥ 1/10000 (0.01%) and < 1/1000 (0.1%)
Very rare:	< 1/10000 (0.01%)
Not known:	(cannot be estimated from available data).

Cardiovascular system
Common: bradycardia, hypotension, sometimes severe; ST segment depression on ECG; sustained or non-sustained ventricular tachycardia; A-V block.
Uncommon: bradycardia, sometimes severe.
Not known: sinus tachycardia; atrial fibrillation; ventricular fibrillation; asystole/cardiac arrest, sometimes fatal, especially in patients with underlying ischemic heart disease/cardiac disorder; MI/ST segment elevation, especially in patients with pre-existing severe CAD; cerebrovascular accident/transient ischemic attack, secondary to the hemodynamic effects of adenosine including hypotension; arteriospasm coronary which may lead to myocardial infarction.

Respiratory system
Very common: dyspnoea (or the urge to breathe deeply).
Rare: bronchospasm; nasal congestion.
Very rare: respiratory failure.
Not known: apnoea/respiratory arrest.

Central nervous system
Very common: headache.
Common: dizziness, light-headedness; paraesthesia.
Rare: tremor; drowsiness.
Not known: loss of consciousness/syncope; convulsions, especially in predisposed patients.

Gastrointestinal system
Very common: abdominal discomfort.
Common: dry mouth.
Uncommon: metallic taste.
Not known: nausea, vomiting.

Other
Very common: flushing; chest pressure/pain, feeling of thoracic constriction/oppression.
Uncommon: sweating; feeling of general discomfort/weakness/pain; nervousness.
Rare: blurred vision; tinnitus; urinary urgency; nipple discomfort.
Very rare: injection site reactions.
Not known: anaphylactic reaction (including angioedema and skin reactions such as urticaria and rash).

Post-marketing experience
In post-market clinical experience with adenosine, sinus tachycardia, atrial fibrillation, and ventricular fibrillation have been reported. Cases of asystole/cardiac arrest, sometimes fatal, especially in patients with underlying ischaemic heart disease/cardiac disorder have been reported (see section 4.4).

Loss of consciousness/syncope, and convulsions especially in predisposed patients have been reported (see section 4.4).

Apnoea/respiratory arrest, and respiratory failure (see section 4.4) have been reported. Cases of fatal outcome of respiratory failure, of bronchospasm, and of apnoea/respiratory arrest have also been reported.

Cases of nausea and/or vomiting have been reported.

More rarely observed side effects have included palpitations, hyperventilation, discomfort in the leg, arm or back. Severe bradycardia has been reported and some patients have required temporary pacing. The effects of adenosine are not blocked by atropine. Asystole, respiratory failure and injection site reactions have been reported very rarely.

Myocardial infarction and ST segment elevation have been reported, especially in patients with pre-existing severe coronary artery disease.

There have been reports of cerebrovascular accident/transient ischemic attack, secondary to the haemodynamic effects of adenosine including hypotension.

Anaphylactic reactions including angioedema and skin reactions such as urticarial and rash have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

As the half-life of adenosine is very short (less than 10 seconds), adverse effects of adenosine are generally rapidly self-limiting. Methylxanthines, such as caffeine and theophylline, and aminophylline are competitive antagonists of adenosine. Intravenous aminophylline or theophylline may be needed.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group Other cardiac preparations

ATC code C01EB10

Mechanism of action

Adenosine is a potent vasodilator in most vascular beds, except in renal afferent arterioles and hepatic veins where it produces vasoconstriction. Adenosine is thought to exert its pharmacological effects through activation of purine receptors (cell-surface A1 and A2 adenosine receptors).

Although the exact mechanism by which adenosine receptor activation relaxes vascular smooth muscle is not known, there is evidence to support both inhibition of the slow inward calcium current reducing calcium uptake and activation of adenylate cyclase through A2 receptors in smooth muscle cells. Adenosine may also lessen vascular tone by modulating sympathetic neurotransmission. The intracellular uptake of adenosine is mediated by a specific transmembrane nucleoside transport system. Once inside the cell, adenosine is rapidly phosphorylated by adenosine kinase to adenosine monophosphate, or deaminated by adenosine deaminase to inosine. These intracellular metabolites of adenosine are not vasoactive.

Myocardial uptake of thallium-201 is directly proportional to coronary blood flow. Since adenosine significantly increases blood flow in normal coronary arteries with little or no increase in stenotic arteries, adenosine causes relatively less thallium-201 uptake in vascular territories supplied by stenotic coronary arteries i.e.: a greater difference is seen after adenosine between areas served by normal vessels and areas served by stenotic vessels than is seen prior to adenosine.

Haemodynamics

Adenosine produces a direct negative chronotropic, dromotropic and inotropic effect on the heart, presumably due to A1-receptor agonism, and produces peripheral vasodilation, presumably due to A2-receptor agonism. The net effect of adenosine in humans is typically a mild to moderate reduction in systolic,

diastolic and mean arterial blood pressure associated with a reflex increase in heart rate. Rarely, significant hypotension and tachycardia have been observed.

Clinical efficacy and safety

The use of adenosine as a coronary vasodilator for use in radionuclide myocardial perfusion imaging was demonstrated in two pivotal active-controlled cross-over studies. Additional supporting data for both efficacy and safety are available in both published and unpublished studies.

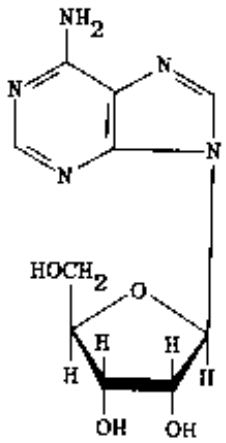
The pivotal studies were conducted in 319 patients in 18 centres. Intravenous adenosine was compared to exercise in non-invasive assessment of coronary artery disease by single photon emission computed tomography (SPECT). In healthy subjects and patients with proven coronary artery disease adenosine was infused at 140 µg/kg/min over 6 minutes. Thallium-201 was given at the midpoint of the infusion. All subjects also underwent standard exercise testing with thallium-201 given one minute prior to the end of the test. Adenosine and exercise thallium images were compared by blinded observers. The images were concordant for the presence of perfusion defects in 85.5% of cases by global analysis (patient by patient) and up to 93% of cases based on vascular territories. These studies confirmed that adenosine infused at a dose of 140 µg/kg/min over 6 minutes produced tomographic cardiac images comparable to exercise thallium. In neither of these studies were other dosage regimens of adenosine nor other imaging agents used.

In a clinical safety study designed to resemble the actual clinical setting for use with adenosine in radionuclide myocardial perfusion over 14,000 patients were infused with adenosine. In this study, thallium-201 was used in approximately 80% of patients, whilst other imaging agents such as technetium 99m-sestamibi, nitrogen-13 and rubidium accounted for approximately 14%, 3% and less than 1% of usage respectively. Imaging was successfully completed in over 98% of the patients and the safety of adenosine with these imaging agents demonstrated. Again the dose of adenosine infused in this study was 140µg/kg/min over 6 minutes.

A dose-finding study, using intra-coronary Doppler flow catheter measurements, demonstrated that intravenous adenosine given at a dose of 140µg/kg/min produced greater coronary artery dilation than lower doses. Higher doses were not studied.

Physicochemical properties

Adenosine is designated chemically as 6-amino-9-β-D-ribofuranosyl-9H-purine and has the following chemical structure:



Adenosine is a white crystalline powder slightly soluble in water.

Molecular weight 267.2

Emperical formula $C_{10}H_{13}N_5O_4$

CAS number 58-61-7.

5.2 Pharmacokinetic properties

Adenosine is a naturally occurring nucleoside which is present in various forms in all cells of the body. It is an essential component of the energy production and utilisation systems of the body.

Adenosine has properties which make it essentially impossible to perform classic ADME studies in man. As a result of an extremely efficient reuptake system in the body, the half-life of intravenously administered adenosine is estimated to be less than 10 seconds. In addition, because adenosine is present in every cell of the body, any administered dose is minute in comparison to the existing body pool.

The metabolic pathways for adenosine have been clearly defined by many investigators. Adenosine may be converted to its base, adenine, and then to AMP; or directly to AMP. Adenosine may also be deaminated to inosine and then converted to AMP. Under normal circumstances, adenosine is generated by the breakdown of ATP and biosynthesis in the liver. It has been suggested that the erythrocytes serve as the transporting vehicle to move adenosine from the liver to those tissues which do not synthesise it. The basic biochemical pathways seem to be the same in all animals, although the relative participation of the various enzymes involved may vary from tissue to tissue.

As might be anticipated for such a biologically important compound, a very efficient system exists to conserve and recycle adenosine in the body. The so-called salvage system for free adenosine in the body is very extensive and effective. The major components of this system appear to be the endothelial cells of the blood vessels and the erythrocytes themselves. An intravenous injection of adenosine, therefore, is placed directly in contact with those cells which most avidly take it up and convert it to a derivative. The *in vitro* half-life of adenosine in whole blood has been estimated to be 9.5 seconds. However, the actual half-life after an intravenous injection is probably shorter that this, since no endothelial cells were present in the blood experimental system.

As adenosine requires no hepatic or renal function for its activation or inactivation, hepatic and renal failure would not be expected to alter its effectiveness or tolerability.

5.3 Preclinical safety data

Carcinogenicity

Studies in animals have not been performed to evaluate the carcinogenic potential of adenosine.

Mutagenesis

Adenosine tested negative for mutation in the Salmonella/Mammalian Microsome Assay. Adenosine, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride	9mg/mL
Water for injections	q.s. to 30mL
Nitrogen	q.s.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened

24 months. The expiry date can be found on the packaging.

Opened

The product should be used immediately after opening.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate.

6.5 Nature and contents of container

Glass type I clear vials (10mL) sealed with chlorobutyl rubber closures.
Packs of 5 or 10 vials packed in a tray in a cardboard carton.

6.6 Special precautions for disposal and other handling

Any portion of the vial not used at once should be discarded. Product is for single use in one patient only.
Discard any residue.

7 MEDICINE SCHEDULE

Prescription only medicine.

8 SPONSOR

ADENOSINE BAXTER is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

ADENOSINE BAXTER is distributed in Australia by:
Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie
NSW 2146, Australia

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
31 August 2017.

10 DATE OF REVISION OF THE TEXT

11 January 2024.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Headings, formatting, spacing, correct usage of trade name.
4.4	Subheadings for Hepatic impairment, Renal impairment, Use in elderly and Effects on laboratory tests included.
4.8	Addition of adverse effects under Cardiovascular system, Respiratory system, Central nervous system, Gastrointestinal system, and Other. Reporting of suspected adverse reactions url updated.
5.1	Inclusion of Thermotherapeutic group and ATC code. Clinical efficacy and safety included. Physicochemical properties included. Text relocated from 5.3
5.3	Carcinogenesis, mutagenesis moved to 5.3.
6.3	Included statement that expiry date can be found on packaging
6.6	Other handling information included.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.