SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Adenosin Life Medical, 5 mg/ml, solution for injection/infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 5 mg adenosine.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/ infusion.

Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Termination of paroxysmal supraventricular tachycardia (PSVT) involving the AV-node.
Induction of brief AV-block for detection and location of accessory pathways with preexitation.
Pharmacological provocation of ischemia in the heart in conjunction with myocardial radio-isotope scanning (thallium or technetium) in patients who cannot exercise adequately or for whom exercise is inappropriate. It can also be used in conjunction with echocardiography in cases where other pharmacological stress agents are not applicable.

4.2 Posology and method of administration

Intravenous injection: *Adenosin Life Medical* is intended for use only in emergency wards, intensive care units, or the equivalent, under continuous monitoring of cardiac rhythm. The dosage instructions below apply to administration via a peripheral vein. Adenosine should be administered by rapid intravenous (IV) bolus injection into a vein or into an IV line. If given into an IV line it should be injected through as proximally as possible and followed by a rapid saline flush. If administered through a peripheral vein, a large bore cannula should be used. Considering adenosine's extremely short elimination half-life, the initial dose should be reduced by approximately 50% if the drug is administered via a central vein.
Intravenous infusion: The investigation should be carried out by a physician with the necessary specialist knowledge and with equipment for acute cardiac care within reach.
To avoid possible bolus effects, the infusion should be given in a separate intravenous line.
Blood pressure should be measured on the opposite arm of that with the adenosine infusion.

Dosage. Treatment of paroxysmal supraventricular tachycardia, PSVT.

Adults: Initially 5 mg is given as a rapid intravenous injection over 1-2 seconds followed by flushing with physiological saline (approximately 5 ml). If necessary, a further dose of 10 mg (followed by a saline flush) may be administered after 1-2 minutes. If the required result is still not obtained, the dose may be increased once again until AV-block is achieved.

Treatment may be repeated twice at 1-2 min intervals. Doses greater than 15 mg are usually not required.
Infants, children and adolescents: Treatment should be carried out under specialised conditions. Cardio-respiratory resuscitation equipment must be available for immediate use if necessary. Adenosine is intended for use with continuous ECG monitoring during administration. The dosage of *Adenosin Life Medical* should be related to body weight and administered in increasing doses, followed by flushing with physiological saline.
The recommended dosing is:

- First bolus of 0.1 mg/kg body weight (maximum dose of 6 mg)
- Increments of 0.1 mg/kg body weight as needed to achieve termination of supraventricular tachycardia

If the reversion to sinus rhythm does not last the treatment can be repeated. Doses greater than 12 mg are routinely not recommended.

Induction of brief AV-block for detection and location of accessory pathways with preexitation.

Adults: Individual dose-titration by rapid i.v. injections (from 5 to 15 mg in adults) in order to obtain shortlasting (<10 sec) AV-block. Treatment may be repeated at 1-2 min intervals.
Infants, children and adolescents: The same safety precautions as for treatment of PSVT should be applied. The dosage of *Adenosin Life Medical should* be related to body weight and administered in increasing doses, followed by flushing with physiological saline. Initially a dose of 50 µg/kg bw should be given. Then the dose can be increased every two minutes by 50 µg/kg bw with each dose step (i.e. 100, 150, 200, 250, 300 µg/kg bw) until a transient effect on AV conduction is seen. Doses greater than 15 mg are usually not required.

As it may be difficult to dose volumes below 0.1 ml exactly, it is recommended that *Adenosin Life Medical* is diluted to 2.5 mg/ml for babies below 5 kg. *Adenosin Life Medical* is preferably diluted with physiological saline (1 part *Adenosin Life Medical* + 1 part saline).

Number of ml of diluted solution (2.5 mg/ml) for children:

Body	Dose level (µg/kg)					
weight (kg)	50[1)]	100	150[1)]	200	250[1)]	300
1	0,02	0,04	0,06	0,08	0,10	0,12
2	0,04	0,08	0,12	0,16	0,20	0,24
3	0,06	0,12	0,18	0,24	0,30	0,36
4	0,08	0,16	0,24	0,32	0,40	0,48
5	0,10	0,20	0,30	0,40	0,50	0,60
>5	---------- undiluted solution ----------					

Number of ml of undiluted solution (5 mg/ml) for children:

Body	Dose level (µg/kg)					
weight (kg)	50[1)]	100	150[1)]	200	250[1)]	300
10	0,10	0,20	0,30	0,40	0,50	0,60
15	0,15	0,30	0,45	0,60	0,75	0,90
20	0,20	0,40	0,60	0,80	1,00	1,20
25	0,25	0,50	0,75	1,00	1,25	1,50
30	0,30	0,60	0,90	1,20	1,50	1,80
35	0,35	0,70	1,05	1,40	1,75	2,10
40	0,40	0,80	1,20	1,60	2,00	2,40

45	0,45	0,90	1,35	1,80	2,25	2,70[2)]
50	0,50	1,00	1,50	2,00	2,50[2)]	3,00[2)]

[1)] PSVT indication: initial dose 100 µg/kg and thereafter, if needed, increments in steps of 100 µg/kg

[2)] PSVT indication: Doses greater than 12 mg are routinely not recommended

Children weighing more than 50 kg can be treated using adult dosage.

Pharmacological provocation of ischemia in the heart in conjunction with myocardial radio-isotope scanning (thallium or technetium) or echocardiography. Adenosin Life Medical is infused intravenously via a peripheral vein. Normally the infusion rate should be 140 µg/kg/min. In scanning adenosine is given during 4-6 minutes and the relevant isotope is injected after 3 minutes of adenosine infusion. Normally the infusion is continuing 2 minutes after the isotope has been injected. In order to reduce the side effects, the infusion can be combined with concomitant low intensity exercise.

Number of milliliters of *Adenosin Life Medical* given per minute at different body weights:

Body weight, kg	ml/min
40	1,1
50	1,4
60	1,7
70	2,0
80	2,2
90	2,5
100	2,8
110	3,1
120	3,4
130	3,6
140	3,9
150	4,2

If there is a pronounced fall in blood pressure (more than 25% of the baseline blood pressure), then dose reduction should be considered (a stepwise reduction of 30 µg/kg/min in one-minute intervals is recommended) in order to avoid further falls in blood pressure.

4.3 Contraindications

Hypersensitivity to adenosine or mannitol. Previous adverse reactions to adenosine. AV-block II and III and sick sinus syndrome in patients who do not have a functioning pacemaker. Severe hypotension. Unstable angina pectoris. Decompensated heart failure.

Only for infusions: Raised intracranial pressure. Hypovolaemia. Concomitant treatment with dipyridamole.

4.4 Special warnings and precautions for use

Because *Adenosin Life Medical* can cause a noticeable hypotension, it should be administered with caution to patients with uncorrected hypovolaemia, trunk stenosis, left/right shunt, pericarditis, pericardial effusion, autonomous nervous system disorder or carotid stenosis with

cerebral vascular insufficiency. *Adenosin Life Medical* should be administered with caution to patients after myocardial infarction.
Adenosin Life Medical should be applied with caution as an infused diagnostic in patients with low-grade conduction pathway disorders (first degree AV-block, bundle-branch block), because a temporary deterioration may occur during the infusion. Patients with atrial fibrillation/flutter and an accessory by-pass tract may develop increased conduction down the anomalous pathway. In patients with chronic obstructive pulmonary disease, adenosine may precipitate or aggravate bronchospasm.
Severe bradycardia has been reported in rare cases. A severe bradycardia should be considered to be a warning that disturbances in formation of impulses and/or conduction system exists. The treatment should be discontinued. A severe bradycardia would particularly support torsades de pointes in patients with prolonged QT interval. In these patients, adenosine given by injection should be used with caution. However, up to date no case of Torsade de Pointes has been reported when adenosine is continuously infused in connection with stress test. The explanation might be the much lower dose given per time unit when infusing adenosine for stress test purposes compared to injection of adenosine for therapeutical reasons.

An increased sensitivity of the heart to adenosine has been observed in patients in which a heart transplantation has recently been performed (within the last year).

Paediatric population
The efficacy of intraosseus administration has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Adenosine interacts with dipyridamole, caffeine and theophylline. Concomitant treatment with theophylline may have the effect that the patient needs a somewhat higher dose to induce AV-block. Caffeine is a weak adenosine receptor antagonist, which means that inter-individual variations in dose requirements may appear in conjunction with caffeine ingestion. Caffeine containing food and beverages should preferably not be ingested for 12 hours before diagnostic use of adenosine.

4.6 Fertility, pregnancy and lactation

Data on a limited number (33, whereof 3 treated in the first trimester) of exposed pregnancies indicate no adverse effects of adenosine on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Caution should be exercised when treating pregnant women and more thoroughly studied and safer alternatives should be considered first.

It is unknown whether adenosine is excreted in human milk. Due to the short half-life of adenosine no risk to the child is anticipated. Adenosin Life Medical can therefore be used during breast-feeding.

4.7 Effects on ability to drive and use machines

No special precautions.

4.8 Undesirable effects

Intravenous injection: Any side-effects are mild and disappear rapidly (usually within 30 seconds). The most common adverse events are dyspnoea (approx. 17%), flushing (approx.

17%) and chest discomfort (approx. 14%). Approximately 50% of patients experience no symptomatic side effects.

	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
General disorders and administration site conditions	Headache, vertigo, chest pains	Perspiration.		
Cardiac disorders	Flush, reflex tachycardia.	Palpitations, hypotension.	Marked hypotension and arrhythmias including ventricular fibrillation. Ventricular extra systolic beats and atrial fibrillation	Arteriospasm coronary which may lead to myocardial infarction.
Gastrointestinal disorders	Nausea.	Metallic taste, pressure in the groin.		
Respiratory, thoracic and mediastinal disorders	Dyspnoea, chest pressure.	Hyperventilation.	Aggravation of bronchial asthma.	
Psychiatric disorders		Agitation		
Nervous system disorders	Paraesthesiae.			
Eye disorders		Blurred vision		

Intravenous infusion:

Intravenous infusion causes a higher frequency of side-effects. However, most are mild and disappear rapidly (within a few minutes). The most common side-effect is chest pain (approx. 40%). In order to reduce the side effects, the infusion can be combined with concomitant low intensity exercise.

	Common (≥1/100 to <1/10)	Uncommon (≥ (1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)

General disorders and administration site conditions	Pain in the head, chest and jaw, vertigo.			
Cardiac disorders	Flush, AV Block I-II, ST-depression	Palpitation, hypotension, AV Block III.	Marked hypotension and ventricular arrhythmias including ventricular fibrillation. Ventricular extra systolic beats and atrial fibrillation.	Arteriospasm coronary which may lead to myocardial infarction.
Gastrointestinal disorders	Nausea, epigastric pain.			
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Hyperventilation.	Bronchospasm	

Rare cases of bronchospasm (also severe) have occurred even in patients not suffering from bronchial asthma or obstructive pulmonary disease.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.
<[To be completed nationally]>

4.9 Overdose

Adenosin Life Medical should be used only in clinics where there is careful monitoring of patients so that overdosage in the normal meaning of the word does not take place. However, severe symptoms associated with side-effects can be treated with aminophylline if reduction of the dose of *Adenosin Life Medical* does not help. Clinical experience has shown that aminophylline treatment is rarely required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cardiac preparations, ATC-code: CO1E B10

Adenosine is an endogenous nucleoside found in all the cells of the body. The effects of adenosine are mediated via purine-1-receptors (P_1-receptors). The effects of adenosine include inhibition of both cardiac conduction time in the AV node and in sinoatrial node as well as a relaxing effect on vascular muscle cells, particularly in arterioles. Adenosine may inhibit conduction in the AV node, which breaks re-entry tachycardia involving the AV node and thus restores normal sinus rhythm in patients with supraventricular tachycardia including

those with the WPW-syndrome (Wolff-Parkinson-White). Treatment with adenosine does not inhibit the conduction time in accessory conduction pathways. The duration of the effect on AV conduction is extremely short (approx. 30 seconds) in the case of intravenous injection. In patients with the WPW-syndrome and antedromic conduction via the accessory pathway, maximum pre-excitation is achieved when the AV node is blocked by administration of adenosine.

Maximal preexcitation recorded using 12-lead ECG may be used to locate the accessory pathway. In patients with intermittent normal electrocardiograms, adenosine may be administered to detect preexcitation.

Adenosine's potent vasodilatory properties in resistance vessels in the heart cause a dose-dependent vasodilation chiefly in non-arteriosclerotic vascular beds. This means that intravenous infusion of adenosine will produce a redistribution of the blood flow from arteriosclerotic vascular beds to more normal areas beds (coronary steal phenomenon) in patients with cardiosclerosis. At the same time, adenosine's general vasodilatory effect brings out a reflexogenic increase in the inotropic and chronotropic effects of the heart leading to increased cardiac work.

Paediatric population

Solution for injection

No controlled studies have been conducted in paediatric patients with adenosine for the conversion of paroxysmal supraventricular tachycardia (PSVT). However, the safety and efficacy of adenosine in children aged 0 to 18 years with PSVT is considered established based on extensive clinical use and literature data (open label studies, case reports, clinical guidelines).

Literature review identified 14 studies where IV adenosine was used for acute termination of supraventricular tachycardia (SVT) in around a total of 450 paediatric patients aged 6 hours to 18 years. Studies were heterogenic in terms of age, and dosing schedules. SVT was terminated in 72 to 100% of cases in most of the published studies. Dosages used varied from 37.5 mcg/kg to 400 mcg/kg. Several studies discussed a lack of response to starting doses less than 100mcg/kg.

Depending on the child's clinical history, symptoms and ECG diagnosis, adenosine has been used in clinical practice under expert supervision in children with stable wide-QRS complex tachycardia and Wolff-Parkinson-White syndrome however the currently available data does not support a paediatric indication. In total 6 cases of adenosine-induced arrhythmias (3 atrial fibrillation, 2 atrial flutter, 1 ventricular fibrillation) have been described in 6 children aged 0 to 16 years with manifest or concealed WPW syndrome, of which 3 spontaneously recovered and 3 needed amiodarone +/- cardioversion.

Adenosine has been used as an aid to diagnosis of broad or narrow complex supraventricular tachycardias in same doses as for treatment of supraventricular tachycardia. Although adenosine will not convert atrial flutter, atrial fibrillation or ventricular tachycardia to sinus rhythm, the slowing of AV conduction helps diagnosis of atrial activity. However, the currently available data does not support a paediatric indication for the use of adenosine for diagnostic purposes.

Solution for infusion

Literature review identified three studies where intravenous adenosine infusion was used in

conjunction with radionuclide myocardial perfusion imaging at a dose of 0.14 mg/kg body weight/min for 2-4 minutes in paediatric patients aged 1 month to 18 years. The largest study included 47 patients aged 1 month to 18 years of age and reported 87% sensitivity (CI 52-97%) and 95% specificity (CI 79-99%) for cardiovascular magnetic resonance imaging under pharmacological stress with intravenous adenosine in a dose of 0.14 mg/kg/min for 3 minutes. No adverse events were reported in the study. However, the currently available data is considered very limited to support the use of adenosine for diagnostic purposes in the paediatric population.

5.2 Pharmacokinetic properties

Exogenously administered adenosine disappears rapidly from the circulation, primarily via cellular uptake, but also by metabolism. Adenosine is eliminated partly by phosphorylation in blood and endothelial cells into adenosine AMP (monophosphate) and further to ADP and ATP, partly by deamination to inosine, which in turn is metabolised to hypoxanthine, xanthine and the final product uric acid. In *in vitro* tests using human blood, adenosine had a plasma half-life of less than 10 seconds (partly dependent on the haematocrit of the blood) so that all the customary pharmacokinetic parameters could not be measured. A small amount of adenosine may be excreted via the urine but the main portion is excreted as adenosine metabolites.

5.3 Preclinical safety data

Because adenosine is naturally present in all living cells, studies in animals to evaluate the carcinogenic potential have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients in 1 ml of (isotonic) *Adenosin Life Medical* are 50 mg mannitol and water for injection.

6.2 Incompatibilities

Adenosin Life Medical must not be mixed with other medicinal products except those mentioned in section 4.2 and 6.6.

6.3 Shelf-life

Unopened packs: 5 years.
After opening or following reconstitution: For immediate and single use only.

6.4 Special precautions for storage

Do not refrigerate or freeze.

6.5 Nature and content of container

10 ml and 50 ml:	injection vials (clear glass, Type I) with rubber stopper (brick-red chloro butyl rubber)
1x10 ml, 10x10 ml, 1x50 ml, 10x50 ml	
2 ml:	ampoules (clear glass, Type I)

10x2 ml

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Can be mixed with 0.9% NaCl solution, see section 4.2

The solution should be inspected visually for particulate matter and discoloration prior to administration. Do not use if cloudiness or precipitate is observed. If crystallisation has occurred, dissolve crystals by warming at room temperature. The solution must be clear at the time of use.

From a microbiological point of view, the product should be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

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

7 MARKETING AUTHORISATION HOLDER

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182 12 Danderyd
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8 MARKETING AUTHORISATION NUMBER(S)

19361

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2003-06-06 / 2014-11-11

10 DATE OF REVISION OF THE TEXT

2023-09-07