

SUMMARY OF THE 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 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 preexcitation.
Pharmacological provocation of ischemia in the heart in conjunction with myocardial radioisotope scanning (thallium or technetium) or 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. 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. 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 or until there is a reversion to normal sinus rhythm. If the reversion to sinus rhythm does not last the treatment can be repeated. 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 weight (kg)	Dose level (µg/kg)					
	50	100	150	200	250	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 weight (kg)	Dose level (µg/kg)					
	50	100	150	200	250	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
50	0,50	1,00	1,50	2,00	2,50	3,00

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

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

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 dosages as for treatment of PSVT.

Pharmacological provocation of ischemia in the heart in conjunction with myocardial radioisotope 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:

<u>Body weight, kg</u>	<u>ml/min</u>
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).

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 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 \geq (1/100, <1/10)	uncommon \geq (1/1,000, <1/100)	rare \geq (1/10,000, <1/1,000)
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
Gastrointestinal disorders	Nausea.	Metallic taste, pressure in the groin.	

	common \geq (1/100, <1/10)	uncommon \geq (1/1,000, <1/100)	rare \geq (1/10,000, <1/1,000)
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 \geq (1/100, <1/10)	uncommon \geq (1/1,000, <1/100)	rare \geq (1/10,000, <1/1,000)
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.
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.

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.

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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8 MARKETING AUTHORISATION NUMBER(S)

19361

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

2008-06-25