All redactions proposed under Sections 40 (Personal information), 41 (Information provided in confidence) and 43 (Commercial interests)

B

COMMERCIAL IN CONFIDENCE

APPLICATION FOR A

PRODUCT LICENCE

PROPOSED CERTIFICATE/LICENCE HOLDER:

Sanofi UK Ltd
Floats Road
Wythenshawe
Manchester M23 9NF

MANUFACTURER OF DOSAGE FORM:

[redacted]

LEGAL STATUS: POM

SALE/SUPPLY: Through hospitals and registered clinics

NUMBER: PL 0623/0056

PRODUCT NAME: Krenosin Injection 6mg/2ml

THERAPEUTIC CLASSIFICATION: Antiarrhythmic

RECEIVED: 26 November 1990

MEETING: April 1991

COMMITTEE ON: SAFETY OF MEDICINES

SUB-COMMITTEE ON: SAFETY, EFFICACY AND ADVERSE REACTIONS

CONSIDERATION BY OTHER COMMITTEES: CPS

ASSESSED BY: [redacted]

Short half-life antiarrhythmic for paroxysmal SVT

INDEX

KRENOSIN INTRAVENOUS INJECTION 6MG/2ML

1. Background

Krenosin injection contains the active drug substance adenosine. Adenosine is a purine nucleoside which is found in all cells in the body. The requested indication is for the treatment of paroxysmal supraventricular tachycardia including Wolff-Parkinson-White syndrome. Its mode of action is by way of its negative dromotropic effect on the atrioventricular node.

[redacted]

The product has marketing authorisation in the USA.

2. Legal Status

Prescription Only Medicine.

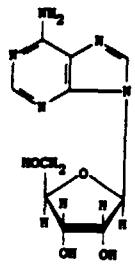
3. Pharmaceutical Comment

Summary

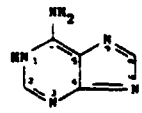
An antiarrhythmic compound which occurs naturally in all cells of the body. The compound has a very short in vivo half life (< 10 seconds) which precludes pharmacokinetic studies. The formulation is a simple solution rendered [redacted] by the incorporation of sodium chloride. [redacted]

The presentation of the main dossier is of an acceptable standard. The main deficiencies relate to points of clarification and justification.

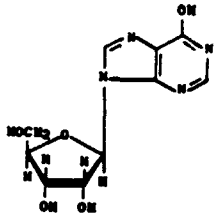
Drug Substance



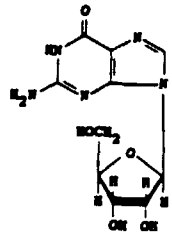
Adenosine



Adenine



Inosine



Guanosine

[redacted]

Satisfactory detailed evidance is presented in the main dossier to support the chemical structure of adenosine. [redacted]

[redacted]

Finished Product

The formulation of Krenosin injection consists of a simple solution of adenosine made [redacted] by the addition of the appropriate amount of sodium

chloride. Satisfactory specifications for water for injections and sodium chloride have been provided. [redacted]

[redacted]

[redacted]

Stability batches have been carried out on product stored in the proposed packaging material [redacted] On the basis of the results obtained, the proposed shelf-life of 24 months is acceptable.

[redacted]

Metabolism and Pharmacokinetics

Due to the extremely brief half-life in vivo (< 10 seconds) and the widespread presence of adenosine occurring naturally in the body, no metabolic or pharmacokinetic studies were undertaken.

Pharmaceutical Recommendation

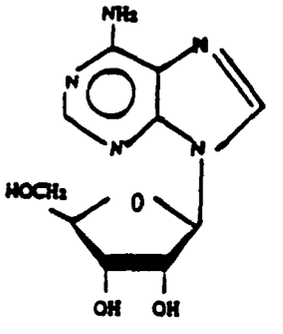
A product licence for Krenosin Injection should not be granted on grounds relating to quality.

[redacted]

PRECLINICAL ASSESSMENT

INTRODUCTION

Krenosin is the Company tradename for adenosine, a purine neucleoside that is an intermediate in the pathway of purine nucleotide degradation. Adenosine is indicated therapeutically for "rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory by-pass tracts (Wolff-Parkinson-White Syndrome)", and diagnostically as an "aid to diagnosis of broad or narrow complex supraventricular tachycardias". Adenosine should be used only when facilities exist for cardiac monitoring. It should be administered by rapid iv bolus injection at an initial dose of 6mg followed by a second dose of 12mg if the first dose does not eliminate the supraventricular tachycardia within one to two minutes. No separate dosing schedule is given for diagnostic use. Krenosin is presented in clear glass injection vials as a 0·3% solution of adenosine (6mg in 2·0ml 0·9% saline solution).



Adenosine, Mwt 267·2

[redacted]

PHARMACOLOGY (Appendix 1, p 23)

No reports of studies specifically conducted to demonstrate anti-arrhythmic activity in animal models have been provided. Instead, the company has relied upon extensive published information on adenosine concerning its cardiac, haemodynamic and other effects.

Since the original report in 1929 on the rapid but transient depressor effect on heart rate caused by intravenously injected adenosine, numerous studies have confirmed and extended these findings. The readily-hydrolysable phosphorylated derivatives of adenosine, particularly ATP, have been shown to possess similar pharmacological effects and it is now generally accepted that their effects are largely or entirely mediated by adenosine.

Adenosine has strong transient negative chronotropic (SA node slowing) and dromotropic (slowing of AV conduction) effects on the mammalian heart. Doses in the range of 0·1 to 0·4mg/kg

are usually sufficient to demonstrate the effects in the live animal (guinea pig, rabbit, cat and dog) though some investigators have used higher doses of up to 2 or 5 mg/kg. Studies with isolated hearts (guinea pig and rabbit) have confirmed the dromotropic effect of adenosine at a concentration of 10^{-7} to 10^{-4} M. Both positive and negative inotropic effects (changes in atrial contractility) have been observed, but the strong negative chronotropic effects of adenosine tend to obscure its inotropic effects. Ventricular anti-arrhythmic effects have been demonstrated in rats and dogs. Intravenously administered adenosine significantly decreased the incidence and severity of early ischaemic arrhythmias in rats subjected to ligation of the left anterior descending coronary artery. In the dog, adenosine perfused into the left ventricle reduced the number of extrasystoles occurring within the first 30 minutes following coronary artery occlusion and reduced the incidence of ventricular fibrillation upon reperfusion of the ischaemic area.

In addition to its electrophysiological effects, adenosine produces pronounced effects on cardiovascular haemodynamics. Intravenous injection of adenosine produces a significant decrease in arterial blood pressure that reaches a maximum in 15-30 seconds, followed by a return to normal values in two to three minutes. Adenosine also affects renal blood flow by causing an initial decrease followed by a reflex increase. Other pharmacological effects have been noted: bronchial effects (bronchoconstriction in the rat), effects on renal function (decrease in glomerular filtration rate) and CNS effects (when administered directly into the brain).

Drug interactions have been noted with nucleoside transport blockers such as dipyridamole which potentiate the negative chronotropic and dromotropic effects of adenosine. Antagonism of the therapeutic effects of adenosine occurs with xanthine derivatives such as caffeine.

PHARMACOKINETICS (Appendix 2, p 32)

No specific pharmacokinetic studies were undertaken by the Company owing to the difficulty in tracking the rapid *in vivo* disappearance from blood plasma of exogenous adenosine.

The biochemical literature indicates that endogenous adenosine levels are maintained at a low steady state concentration (<0·03 to 2·6μM in body fluids) through a balance between cellular release and removal from extracellular space. Adenosine is an important regulator of coronary blood flow being released from the myocardium under conditions of stress or vigorous exercise or during pathological ischaemia. This activity is terminated by removal of adenosine from the receptor by uptake into cells, especially endothelial cells which have an efficient adenosine uptake system. Adenosine in the general circulation is also removed by blood cells (particularly erythrocytes), the lung, the spleen and the liver, as well as being metabolised by extracellular adenosine deaminase. Following uptake into cells adenosine is readily

metabolised by two main routes: deamination to inosine and phosphorylation to AMP.

Bearing in mind the effective removal mechanisms that exist for endogenous adenosine, it is not surprising that intravenously injected adenosine is rapidly cleared from the circulation, a half-life of <10 seconds often being quoted. No in vivo data appear to be available to support this value though adenosine does have a half-life of 9·3 seconds when incubated in vitro in whole human blood. However, the concentration used (10μM) was rather low in comparison with the injected concentration of adenosine (3mg/ml, 11mM) and it is known that concentrations of greater than 200 and 10μM inhibit adenosine deaminase and adenosine kinase respectively. It is concluded that the half-life of adenosine may not be quite as short as 10 seconds.

TOXICOLOGY (Appendices 3 and 4, p34,37)

Acute toxicity

Single intravenous doses of adenosine to groups of mice (240mg/kg; 800xMHD for 60kg patient) and rats (48mg/kg) produced no deaths or other adverse effects during the 14-day observation period (Appendices 3.1 and 3.2). No abnormalities were detected at necropsy. A repeat of these studies at another laboratory using iv doses in mouse and rat of 250 and 50mg/kg respectively, gave no mortalities and no other adverse effects apart from a marked transient prostration during injection in the mouse (Appendix 3.3).

Repeat dose toxicity

Groups of rats were injected intravenously with adenosine at a total dose of 200mg/kg divided into five equal doses of 40mg/kg given at one-minute intervals (Appendix 4.1). Over the next two weeks the animals were subjected to clinical observation, bodyweight, organ weight and food consumption determinations, and analysis of blood and urine parameters, etc. One female died within 30 minutes of treatment with adenosine. Prostration was noted prior to death and red foci were observed in the thymus and left lobe of the lung during necropsy. No microscopic examinations of the affected tissues were undertaken. No cause of death could be established though, as conceded in the expert report, death was almost certainly treatment related. All other animals survived to study termination and no other adverse effects were noted.

A similar study in dogs (Appendix 4.2), using four male and four female animals in the test and control groups, employed a total dose of 50mg/kg divided into five equal doses of 10mg/kg injected at one-minute intervals. The dogs treated with adenosine showed decreased activity and ptyalism in the first hour after dosing. No treatment-related effects were noted during the two-week observation period, nor were any abnormalities or organ weight changes noted at necropsy.

MUTAGENICITY (Appendix 5, p)

The mutagenic potential of adenosine has been evaluated in respect of gene mutations in bacteria (Ames test - in fact two tests were conducted) and unscheduled DNA synthesis in primary rat hepatocyte cultures. The tests were carried out to adequate standards and both gave negative results.

Although the Company has not provided an *in vitro* test for chromosome damage, or any *in vivo* tests, this is probably justified in view of the short half-life and proposed acute use of adenosine.

CARCINOGENICITY

No carcinogenicity studies were submitted. In view of the clinical indications for adenosine, its natural occurrence, low dose and high purity, this is considered acceptable.

REPRODUCTIVE TOXICITY

No reproductive toxicity studies were submitted, being justified by the Company by the fact that adenosine is already present throughout the body, the proposed clinical indications and the extremely short half-life. This is probably acceptable, though a conventional rat teratology study would have been straightforward to perform and would have given considerable reassurance on the foetoxicity of exogenous adenosine.

The pregnancy warning is as follows: "Adenosine is a substance which is naturally present in some form in all cells of the body, therefore no effect on the foetus would be expected. In the absence of evidence that adenosine does not cause foetal harm, Krenosin should only be used during pregnancy where absolutely necessary."

SPECIAL STUDIES (Appendix 6, p 39)

The acute intravenous cardiovascular toxicity of adenosine was investigated in conscious beagle dogs at an initial dose of 4·8mg/kg followed by a second dose of 9·6mg/kg two to three hours later. There was no evidence for cardiovascular toxicity based on a range of parameters including blood pressure and electrocardiographic examination (Appendix 6.1).

A further study was conducted in anaesthetised dogs in order to assess cardiovascular and respiratory tolerance following intravenous injection of adenosine at 4 and 2mg/kg. The parameters measured (both before dosing and several times after dosing) included (for cardiovascular tolerance) blood pressure, heart rate, cardiac output and ECG and (for respiratory tolerance) respiratory frequency, respiratory flow and tidal volume. At both doses transient decreases were noted in blood pressure, left ventricular pressure and peripheral resistance. Recovery occurred after four minutes. Moderate bradycardia and a negative inotropic effect were observed shortly after dosing and recovery occurred gradually

over 15 minutes. There was also a transient increase in respiratory flow and respiratory frequency (Appendix 6.2).

[redacted]

CONCLUSIONS

The studies conducted on adenosine were very limited in number and type, but except for an isolated mortality, no adverse effects occurred in acute studies at doses at least 150 times the maximum therapeutic dose. The abbreviated preclinical evaluation seems to be adequate and the omission of most standard tests can be justified in the light of the clinical indications, apart perhaps from teratogenicity, although clinical experience and an appropriately worded pregnancy warning may well compensate for the absence of animal data.

[redacted]

February 1991

3 MEDICAL COMMENT

3.1 INTRODUCTION

The application is for Krenosin Injection. Each vial contains 6mg adenosine in 2ml saline.

Adenosine is a ubiquitous purine nucleoside present in all cells as a key intermediate in the metabolism of ATP. It is released from a wide variety of tissues under conditions of stress, e.g. hypoxia or energy deficit. By binding to specific receptors present on the membranes of virtually all cells, adenosine modulates the activity of adenylate cyclase and is probably involved in a number of physiological processes. Being a vasodilator in most vascular beds, adenosine may be the mediator involved in matching local blood flow to metabolic demand.

Some drugs, such as methylxanthines, may act through adenosine receptor blockade while others, such as dipyridamole, may exert their effects by blocking adenosine uptake.

Adenosine has been known to affect the electrophysiological properties of cardiac tissue since the 1920s, but only recently has its role in the treatment of supraventricular tachycardias become recognised. Nevertheless, as a biochemical agent adenosine has been readily available for research and this accounts for the large number of published pharmacological and clinical studies which are said to number some 20,000.

3.1.1 Indications

Adenosine is used therapeutically to convert paroxysmal supraventricular tachycardia to sinus rhythm.

By slowing AV conduction it may also help in the electrocardiographic diagnosis of broad or narrow complex tachycardias. Sensitisation during intra-cavitary electrophysiological investigations is also listed as an indication.

3.1.2 Dosage

The initial dose is 6mg given as a rapid iv bolus. If this does not eliminate the SVT within 1 to 2 minutes, 12mg should be given.

For children the dose quoted in the data sheet is between 0·10 and 0·25mg/kg.

3.2 PHARMACODYNAMICS

3.2.1 Electrophysiological Effects

Adenosine has a depressant effect on sinus automaticity and atrioventricular conduction. Bolus injection into normal subjects (100μg/kg) may produce sinus bradycardia, sinus arrest, ectopic atrial rhythms and first, second or third degree heart block but the effects are transient. Usually sinus bradycardia follows 10-20 seconds after injection, lasts less than 10 seconds and is followed by a mild sinus tachycardia. The tachycardia is probably not a delayed effect of adenosine itself as the sinus rate does not change during asynchronous ventricular pacing.

In patients undergoing electrophysiological studies, bolus injection of adenosine (mean dose 180μg/kg) produces sinus node depression and progressive prolongation of atrial-His intervals followed by AV nodal block. Again the effect occurs 10-20 seconds afer injection and is over in less than 10 seconds. Doses effective in terminating supraventricular tachycardia do not necessarily suppress sinus automaticity.

Adenosine has no effect on antegrade conduction over accessory pathways in patients with Wolff-Parkinson-White syndrome. Indeed adenosine increases QRS pre-excitation as the atrial-His interval becomes longer than the AV conduction time over the accessory pathway.

Adenosine is undoubtedly effective in terminating most supraventricular tachycardias and electrophysiological studies show that usually this is achieved by blocking re-entry at the AV node. It follows that adenosine is generally ineffective in terminating dysrhythmias not involving re-entry via the AV node though here it may help ECG diagnosis by transiently blocking AV conduction. Sometimes, however, adenosine may work by blocking conduction in the retrograde limb of a re-entry loop.

Ventricular tachycardia does not normally respond to adenosine, the exception being exercise-induced VT in an otherwise normal heart. Here adenosine may have a quite different mode of action as this arrhythmia is believed to be caused by cyclic AMP-mediated triggered activity. Also, adenosine has no direct electrophysiological effect on the ventricular myocardium in contrast to supraventricular tissue, where it increases potassium conductance.

3.2.2 Cardiovascular Effects

Adenosine is a vasodilator in most vascular beds and, in anaesthetised patients, iv infusions produce a significant (35mmHg) reduction in blood pressure with only a mild increase in heart rate. On the other hand, in conscious man, steady state iv infusions of adenosine cause a dose related increase in heart rate and systolic pressure with only a slight decrease in diastolic pressure. This difference has been attributed to a blunting of autonomic reflexes in

anaesthetised patients, a view supported by the finding that patients with autonomic failure respond in a similar way. The autonomic stimulus is thought to arise in the region of the carotid body as, in conscious cardiac patients, injection of adenosine into the ascending aorta increases blood pressure and heart rate whereas injection into the descending aorta causes a profound decrease in blood pressure. An effect via the CNS is unlikely as in animals adenosine does not easily cross the blood-brain barrier. Also, effects on breathing are consistent with stimulation of the peripheral chemo-receptor (vide infra).

Given as an iv bolus to normal volunteers (100μg kg) adenosine produces a biphasic blood pressure response with an initial increase (about +15mmHg) occurring at about 27 seconds followed by decrease (about -10mmHg). The trough in blood pressure is accompanied by an increase in heart rate.

Coronary arteries are no exception to the vasodilatory effects of adenosine but when maximum tolerable doses are given as intravenous boluses to normal subjects an angina-like pain may be elicited. The pain is accompanied by a feeling of unease and anxiety. Dipyridamole increases the intensity of the pain; after aminophylline it is less severe. Direct stimulation of adenosine receptors has been suggested as the cause of the discomfort and the implication is that the pain of angina proper may have a similar mechanism - a view which fits the concept of adenosine as a mediator in the control of blood flow in the myocardium. There is no evidence that adenosine ever causes coronary artery spasm. On the contrary, injection of adenosine into human coronary arteries increases blood flow in the great cardiac vein.

3.2.3 Respiratory Effects

Although adenosine relaxes smooth muscle in most tissues, in the airway it may increase tone. In patients with asthma inhaled adenosine causes a dose dependent reduction in FEV_1, but in normal subjects there is no response. A specific pharmacological mechanism rather than non-specific irritation seems likely as similar concentrations of guanosine have no effect. The bronchoconstrictor effect of adenosine is long lasting (>30 min) suggesting that it may act by stimulating the release of other mediators. It is said that intravenous adenosine does not affect airways resistance in asthmatics but, despite their clinical importance, details of such observations are lacking.

Intravenous bolus injections of adenosine cause a dose-related increase in ventilation. The timing of the response suggests that the peripheral chemoreceptor may be involved and consistent with this is the observation that adenosine increases ventilatory sensitivity to hypoxia.

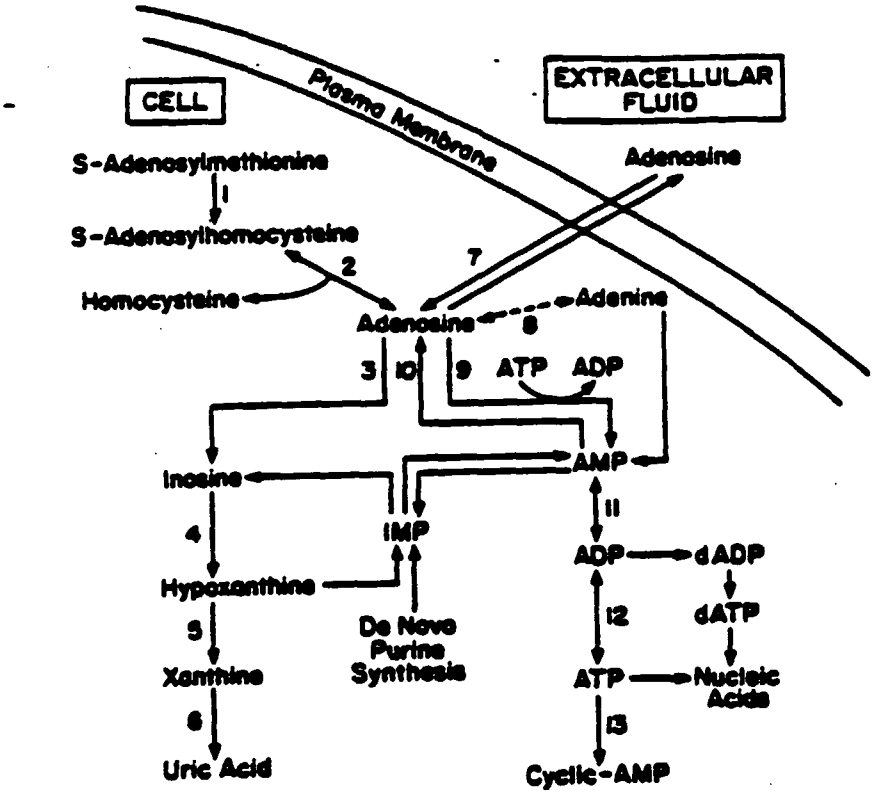
3.2.4 Cell Toxicity and Immunosuppression

Adenosine has toxic effects on cultured mammalian cells and bacteria at concentrations ranging from 1-1000μM. Bacteriostatic effects have been observed in a number of organisms and inhibition of growth in cultured human diploid fibroblasts, human lymphoblasts and other cells. Developing T-cells are believed to be particularly sensitive to adenosine and inhibitors of adenosine deaminase cause immunosuppression in animals. In man adenosine deaminase deficiency is characterised by severe combined immunodeficiency.

The biochemical basis for adenosine toxicity and immunosuppression has been the subject of intensive research. The toxic effects are associated with a block in pyrimidine synthesis and can be reversed with uridine but other mechanisms including a block in purine synthesis are possible.

3.3 PHARMACOKINETICS

Normally plasma levels of adenosine range from 0·02-0·4μM. Even in venous blood draining organs actively producing adenosine plasma concentrations seldom rise above 10μM. Concentrations in the cell cytosol are immeasurable and adenine is readily transported across cell membranes by facilitated diffusion. Consequently, when adenosine is added to whole blood it rapidly enters cells where it may be removed by degradation to purines or synthesised into adenine nucleotides. The metabolism of adenosine is summarised in the diagram below.



The half-life of adenosine when added to whole blood at 37°C in an initial concentration of 10nmol/ml is less than 10 seconds but a longer half-life might be expected with higher concentrations which inhibit adenosine deaminase and adenosine kinase. The half-life of adenosine following iv injection is not known but is said to be less than 10 seconds. Claims in the literature that following intravenous injection 'adenosine is essentially totally cleared from the plasma in less than 30 seconds' are not referenced and appear to be based on the in vitro studies and knowledge of the way in which adenosine is rapidly taken up and metabolised by cells.

Information on plasma levels of adenosine following iv administration is scanty. In anaesthetised patients on clinical doses of dipyridamole infusion rates around 140μg/kg/min give arterial concentrations of approximately 2·5μM. In the absence of dipyridamole doubling the infusion rate produces a similar haemodynamic response but blood levels are not available.

3.3.1 Interactions

In conscious man the cardiovascular effects of an adenosine infusion can be produced by a 4-fold lower dose in the presence of dipyridamole. Similarly, very small doses of adenosine can be effective in treating arrhythmias in patients on dipyridamole while standard doses can induce a profound bradycardia. Theophylline and other xanthines inhibit adenosine but, as with dipyridamole, there is insufficient clinical data to be able to make firm recommendations as to how the dose should be modified to take account of such interactions.

There appear to be no interactions with beta-blockers, digoxin, diuretics or other antiarrhythmic drugs but experience is limited.

Asystole has been reported in one patient who was taking carbamazepine and interaction with other drugs which tend to impair cardiac conduction is a possibility.

3.4 EFFICACY

The dossier contains two pivotal double-blind placebo-controlled trials. For these studies supraventricular tachycardia was defined as an atrial tachycardia which required AV nodal conduction as part of the re-entrant circuit.

A total of 158 patients with spontaneous or induced SVT entered the first trial. In an initial double-blind phase adenosine (6mg IV) was compared with both placebo and verapamil (5mg IV). For non-responders the code was broken and the adenosine group was given a further 12mg adenosine and the verapamil group another 7·5mg verapamil. Any in the verapamil group still failing to convert were then given adenosine.

The first dose of adenosine (6mg) was effective in restoring sinus rhythm in 57% of eligible patients whereas verapamil (5mg) converted 81%. Following the second dose of either adenosine (12mg) or verapamil (7·5mg) the cumulative conversion rate was over 90% for each group. Adenosine acted more quickly than verapamil (50 seconds versus 168 seconds for the 6mg dose, 34 seconds versus 300 seconds at the higher dose). The six verapamil failures all converted with adenosine.

The second double-blind trial was a dose-ranging study comparing sequential doses of 3, 6, 9 and 12mg of adenosine with placebo in the treatment of both spontaneous and induced SVT. The adenosine group numbered 137 and the placebo group 64. The number of patients in whom sinus rhythm was restored is shown for each dose in the table below. If ineligible patients are excluded (24 did not have SVT) the cumulative conversion rate after the 12mg dose goes up to 92%.

Ampoule n°	Adenosine (n = 137) (mg) per dose	sum (%)	Placebo (n = 64) per dose	sum (%)	P
1	3 41/137	41 (29.9)	5/64	5 (7.8)	0.000
2	6 32/ 96	73 (53.3)	1/59	6 (9.4)	< 0.001
3	9 22/ 64	95 (69.3)	2/58	8 (12.5)	< 0.001
4	12 14/42	109 (79.6)	1/56	9 (14.1)	< 0.001

Nine published studies provide supportive evidence of efficacy. In the largest (DiMarco et al, 1985) 46 patients with both spontaneous and induced SVT (including atrial fibrillation, flutter and other tachycardias not dependent on AV nodal re-entry) were given adenosine. In doses ranging from 2 to 23mg, adenosine terminated SVT in all 16 patients with AV reciprocating tachycardia and all 13 patients with AV nodal re-entrant tachycardia. In patients with atrial fibrillation, atrial flutter and intra-atrial re-entrant tachycardia adenosine produced transient AV block.

Sellers et al (1987) gave adenosine to 25 patients with presumed SVT in the emergency room. The study is of value in that it may represent the way in which adenosine is likely to be used in everyday practice - for example, two of the patients actually had ventricular tachycardia and three simply a sinus tachycardia. In these patients adenosine, while ineffective as a treatment, enabled the diagnosis to be made without inducing hypotension. Similarly, adenosine helped in the diagnosis of six episodes of atrial flutter. In the patients with SVT due to Wolff-Parkinson-White syndrome or AV node re-entry adenosine was effective in 18/18 episodes and when, in a separate group of patients, SVT was induced during electrophysiological studies conversion occurred in 25/25 episodes. In this study the dose of adenosine was incremented at one minute intervals until the tachycardia was terminated or side effects limited administration. Effective doses ranged from the starting dose, 0·0375mg/kg, to 0·3mg/kg.

Retrospective comparison with verapamil suggested that adenosine was more effective and faster acting.

Rankih et al (1990a) also compared adenosine retrospectively with verapamil in the treatment of 43 patients with 164 episodes of SVT. Verapamil restored sinus rhythm in 81% of episodes and adenosine in 94%. Fifteen patients were treated with both agents. In 7 of the 15 verapamil failed to restore sinus rhythm at least once whereas adenosine was successful in all. However, early recurrence tended to occur after adenosine occurring in 20/164 episodes. The dosage of adenosine was incremental from 2·5mg to 30mg. The verapamil was administered in 5mg boluses with a maximum cumulative dose of 30mg.

In a double-blind randomized trial Rankin et al (1990b) went on to compare adenosine with ATP in the treatment of both spontaneous and induced arrhythmias. Adenosine restored sinus thythm in 25/27 episodes and in 9 patients produced AV block to reveal atrial tachyarrhythmias. The effects of ATP were similar and the two agents appeared to be of equimolar potency. The mean effective dose of adenosine was 7.3mg (range 2·5-20mg).

In a dose-ranging study on 7 patients with spontaneous SVT, Watt et al (1986) found that the mean effective dose was 8·8mg. One patient on dipyridamole developed a profound bradycardia after a starting dose of 40μg/kg and, in view of this, another patient on dipyridamole was given an initial dose of just 10μg/kg which proved effective. In patients not on dipyridamole the lowest effective dose was 80μg/kg.

[redacted] in a brief but seminal paper (Munoz, 1984) describes his early experience with adenosine which was effective in 8/10 episodes of SVT.

Several authors mention the diagnostic value of inducing transient AV block with adenosine. One paper (Griffiths et al, 1988) specifically considers the use of adenosine in the diagnosis of broad complex tachycardia. These authors found that in 8 of 9 cases of broad complex SVT (all laboratory induced) given adenosine the arrhythmia was terminated, converted into narrow complex SVT or AV block was induced whereas in ventricular tachycardia the arrhythmia was stopped in only 1 out of 17 cases. The authors believe that 'adenosine as a diagnostic agent in cases of broad complex tachycardia should be limited to those in whom the diagnosis is uncertain and in whom immediate direct current cardioversion is not required'. They also state that 'adenosine in irregular broad complex tachycardias is less likely to be helpful and we do not recommend that adenosine is given for the management of irregular tachycardias'. Here, however, it is worth noting that adenosine had no adverse effects on 6 patients with atrial fibrillation and ventricular pre-excitation though there was a transient shortening in RR intervals.

Two papers describe the usefulness of adenosine in the treatment of arrhythmias in infants and children. Clarke et al (1987) successfully terminated resistant SVT in three seriously ill newborn infants and one older child. In a larger study, also uncontrolled, Overholt et al (1988) administered adenosine to 25 infants and children with arrhythmias (11 spontaneous, 14 induced). The effect of adenosine was essentially the same as in adults. The minimum effective dose was 37·5-350μg/kg. The dose for children mentioned in the data sheet seems to be based on the smaller study on just 4 patients.

3.5 SAFETY

In the double-blind studies adenosine was given to 268 patients of whom 102 (38%) experienced one or more adverse events. The commonest was facial flushing (18%), followed by dyspnoea/shortness of breath (12%), chest pressure (7%) and nausea (3%). A similar safety profile emerged from the published data (n=204). The adverse events occurred soon after injection and usually lasted less than a minute but in one patient flushing lasted 7 minutes and in another shortness of breath persisted for 9 minutes.

As sinus rhythm was being restored various electrocardiographic phenomena were reported but since they tended to last for just a few seconds they were not usually of any clinical significance. However, one patient in the placebo/verapamil trial did cause concern. This patient had atrial flutter/fibrillation (in violation of the protocol) and one minute after receiving 12mg adenosine became asystolic. After 5 seconds pacing was commenced until, within a minute, the previous rhythm was restored. Amongst several other drugs, this patient was taking carbamazepine and timolol eye drops.

In the published papers there is a reference to severe but self-limiting bradycardia occurring in a patient on dipyridamole given 40μg/kg and severe sinus bradycardia requiring pacing and lasting <2 to 3 minutes in a boy aged ten given 150μg/kg.

On first principles, it seems that potentially serious bradycadias might be minimised by starting with a lower dose than recommended and gradually titrating up according to the response. However, while there is evidence that a 3mg dose may be effective in more than a third of patients, there are no data to show that individually titrated doses would actually be any safer. Nevertheless, the short half-life of adenosine means that there would be little to lose by adopting such an approach.

It is assumed that in the doses recommended adenosine would not affect laboratory variables. While there is every reason to believe this to be the case there are no clinical data to support this contention.

3.6 DATA SHEET

The diagnostic indications could be more explicit. The phrase 'aid to diagnosis of broad or narrow complex supra-ventricular tachycardias' implies that the distinction from ventricular tachycardia (the main clinical problem) has already been made though the mention of ventricular tachy-cardia in the next sentence suggests that the differential diagnosis of broad complex tachycardia is indeed intended as an indication.

The statement that Krenosin is not effective in ventricular tachycardia, while generally true, is technically incorrect.

It is unclear how adenosine should be used in intra-cavitary investigations.

Under warnings, the possibility that patients with atrial fibrillation/flutter and an accessory by-pass track may develop increased conduction down the anomalous pathway should be mentioned.

Under side effects, it should be made clear that facial flushing, dyspnoea and a feeling of thoracic constriction are commonly reported. The duration of side effects should be changed from 'less than one minute' to 'usually less than one minute'.

It should be emphasised that severe bradycardia may occur and that occasional patients have required temporary pacing.

It is unclear why carbamazepine but not other drugs with a propensity to cause heart block merits inclusion under drug interactions. A general warning concerning possible interaction with drugs tending to depress conduction might be more appropriate.

The warning against using Krenosin during breast feeding unless essential is overcautious. In any case it is the breast feeding that should be restricted rather than the use of Krenosin.

3.7 EXPERT REPORT

A helpful expert report was written by [redacted]

CONCLUSIONS

The potent cardiovascular effects of adenosine have been recognised since the 1920s and since then a considerable amount of information has accrued on its pharmacodynamic effects though its precise physiological role remains uncertain.

Adenosine appears to have a short half-life in vitro but it is difficult to assay and its pharmacokinetics have barely been studied.

Krenosin is undoubtedly effective in the treatment of supraventricular tachycardias involving re-entry via the AV node and is unlikely to cause serious harm if given to patients with other tachycardias. There is little documentation on its use in diagnosis but it could be valuable in broad complex tachycardia to help distinguish supra-ventricular tachycardia from ventricular tachycardia when this is not possible on other criteria.

The short half-life of adenosine means that it is likely to prove safer than alternative agents especially in patients with ventricular tachycardia or other arrhythmias which do not respond but the relapse rate may also be higher.

The use of adenosine in the treatment of supraventricular tachycardias is almost certainly a genuine therapeutic advance and the issuing of a product licence would benefit patients by making a potentially safer agent more widely available. However, the 6mg starting dose seems unnecessarily high when a third of patients will respond to half this dose. Severe bradycardias have occasionally occurred following adenosine and, although there is no evidence that a lower starting dose would be safer, on first principles it should be.

A product licence should be granted provided that the diagnostic indications are omitted, the initial dose is reduced to 3mg and the data sheet is amended.

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