dtd: 05/03/94.
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ABRIDGED PRODUCT LICENCE APPLICATION

PHARMACEUTICAL ASSESSMENT REPORT

LICENCE NO:	**11723/0086**
PRODUCT :	**Adenoscan Solution for Infusion 3mg/ml**
COMPANY :	**Sanofi Winthrop Lts**
EC ARTICLE :	**Hybrid**
LEGAL STATUS:	**POM**

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

1. BACKGROUND

Adenoscan is a 3mg/ml injection of adenosine indicated for use as a coronary vasodilator as an alternative to exercise in radionuclide myocardial perfusion imaging. Adenosine has previously been approved for use in supraventricular tachycardias and as an aid to diagnosis of other tachycardias under the brand name Adenocor, PL/11723/0005. The dose and administration of the two products are quite different although the formulations are qualitatively and quantitatively identical.

2. PART 1 MLA FORMS

1. An amended MLA 201 P. 8 is required with an additional check limit for pH included.

3. PART 2 DOSSIER

Composition

Adenoscan consists of adenosine as the active in a sterile solution containing Sodium Chloride Ph. Eur.(isotoniser) in Water for Injection Ph. Eur. as solvent.

Containers

10ml colourless type I glass vial with a chlorobutyl rubber stopper secured with a crimped aluminium cap.

Clinical Trial Formulation.

Clinical trials were carried out using both the proposed formulation for marketing and a second formulation containing adenosine 6mg per ml. Satisfactory batch analysis data from clinical trial batches has been provided.

Development Pharmaceutics

[redacted] The vial size has, however, been increased from 2ml to 10ml. To validate the increase in fill volume, [redacted]

[redacted]

[redacted] The formulation has been satisfactorily justified.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

In-Process Controls

Satisfactory in-process controls are carried out throughout the manufacturing and sterilisation process.

[redacted]

[redacted]

Method of Sterilisation

See method of manufacture above.

Control of Starting Materials

Active Ingredient

[redacted]

Other Ingredients

Both Sodium Chloride and Water for Injections comply with the Ph. Eur. and satisfactory certificates of analysis have been provided.

Packing Material

Full specifications for the glass vials, rubber stoppers and aluminium caps have been provided. The issues of adsorption of the active ingredient by the stopper and substances leached from the stopper have been satisfactorily dealt with.

Control Tests on Intermediate Products

Not applicable.

Control Tests on the Finished Product

[redacted]

All test and assay methods have been fully described and validated.

[redacted]

Stability

[redacted]

Bioequivalence

Not applicable.

Product Particulars

This application was received before 1 January 1994, so that the product particulars do not have to comply with the new regulations.

The proposed carton text is satisfactory.

The vial label should be amended to include a statement to the effect that any remaining solution should be discarded

The PIL should be amended to give the correct name and address of the manufacturer in line with MLA 201 P. 11

An SPC has not been provided.

4. PHARMACEUTICAL RECOMMENDATION

A product licence may be granted for this product provided that all outstanding pharmaceutical issues are satisfactorily addressed.

[redacted]

B1A
10 March 1998 4?

PL/11723/0086 ADENOSCAN SOLUTION FOR INFUSION 3MG/ML SANOFI WINTHROP.

SECTION 44 POINTS

1. [redacted]

2. [redacted]

3. [redacted]

4. The vial label should be amended to include a statement to the effect that any solution remaining after use should be discarded.

5. The Patient Information Leaflet should be amended to include the correct name and address of the manufacturer as given on MLA 201 P.11.

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PL/11723/0086 ADENOSCAN SOLUTION FOR INFUSION 3MG/ML SANOFI WINTHROP.

REPLY TO A SECTION 44 LETTER DATED 17 NOVEMBER 1994

Q1. [redacted]

[redacted]

Q2. [redacted]

[redacted]

Q3. [redacted]

[redacted]

Q4. ***The vial label should be amended to include a statement to the effect that any solution remaining after use should be discarded.***

A. The label has been satisfactorily amended. This point is cleared.

Q5. ***The Patient Information Leaflet should be amended to include the correct name and address of the manufacturer as given on MLA 201 P.11.***

A. The PIL has been satisfactorily amended. This point is cleared.

PHARMACEUTICAL RECOMMENDATION.

A product licence may be granted for this product.

[redacted] 16 March 1995

dtd: 10/11/94.

(13A)

MEDICAL ASSESSMENT REPORT

PRODUCT LICENCE NUMBER	11723/0086
PRODUCT NAME	ADENOSCAN
ACTIVE	Adenosine
COMPANY	Sanofi Winthrop
EEC ARTICLE	4.8(a)(iii)
LEGAL STATUS	POM

1. INTRODUCTION

Adenosine is an endogenous nucleoside involved in many biological processes. It acts as an anti arrhythmic by slowing conduction through the atrioventricular node. It is also a potent vasodilator in most vascular beds (not renal or hepatic, though) through activation of α and $\alpha 2$ adenosine receptors.

Adenosine is licensed as an anti arrhythmic agent by the present applicant who is now seeking an extension to its indications for use which involves a different dosage schedule and patient population.

The new indication which is sought is as a coronary artery vasodilator for use as an alternative to exercise in conjunction with radionuclide myocardial perfusion imaging. The dose schedule is a continuous 6 minute intravenous infusion at 140µ/kg/min which exposes patients to higher doses, over a longer period, than the present approved dosage which is up to three consecutive bolus intravenous injections (3, 6, and 12mg).

2. BACKGROUND

Elf Sanofi were granted PL 0623/0056 on 14 August 1991 for Krenosin (Adenosine Injection 6mg/2ml). Subsequently the name has changed to Adenocor and the licence transferred to Sanofi Winthrop (PL 1172/0005).

3. INDICATION

See MLA 201. For use as an alternative to exercise in conjunction with radionuclide myocardial perfusion imaging.

4. DOSE AND DOSAGE SCHEDULE

See MLA 201. Hospital use only; constant monitoring; continuous infusion of 6 minutes with radionuclide injected after 3 minutes. Adequate instructions and advice are contained in the product literature.

5. TOXICOLOGY

Toxicology evaluation has already been fully documented for adenosine (Adenocor). Since the administration of Adenoscan will be by a continuous infusion rather than by short term single or repeat dose injections, an additional dog toxicology study has been conducted in which the effects of long term repeated infusions have been evaluated.

Two groups of two dogs (1M, 1F) received either a continuous 32h infusion of 280μ/kg/min ie. twice the human recommended rate, or repeated 3h infusions over 7 days at increasing rates (140 to 1400μ/kg/min).

Various non specific clinical signs were observed: trembling, relaxed nictitating membrane, injection of sclera, decreased activity (repeat dose dogs), vaginal discharge, twitching of legs with decreased activity (continuous infusion dogs).

No hypotension and only sporadic instances of ventricular dysrhythmias were observed.

6. CLINICAL PHARMACOLOGY

The very short half life (10 secs) of adenosine precludes the conduct of classical pharmacokinetic studies. However, the potential interaction of adenosine with other drugs has been investigated through published literature and ongoing clinical trial experience with Adenoscan.

Dipyridamole potentiates the action of adenosine whereas methylxanthines such as theophylline are competitive antagonists of adenosine. Aminophylline antagonises the AV block caused by adenosine and may be used to counteract adverse effects. No interactions have been detected between adenosine and digoxin, amiodarone, beta-blockers, quinidine, flecainide, disopyramide or verapamil.

The pharmacodynamic effects of a bolus dose of adenosine (fully described for Adenocor) differ significantly from those of a continuous infusion. These latter effects have been

characterised by published studies conducted in both volunteer subjects and patients and indicate that adenosine infusions product consistent

a) haemodynamic effects: modest increase in heart rate, slight or no decrease in BP, and decrease in SVR.

b) electrocardiographic effects: ST depression, transient AV node conduction delay.

Intracoronary infusion of adenosine produced similar effects (but at lower doses) to intravenous adenosine: increased coronary blood flow velocity or coronary vasodilation was similar to that observed with IC papaverine (reference drug for obtaining maximum coronary flow).

Two Phase 1/11 studies have been conducted. Study [redacted] is important since it provides justification for the choice of the recommended infusion dose level. This was an open, dose response study in 31 patients conducted in the US during 1988-89. Firstly, maximum coronary blood flow was measured by an IC Doppler catheter after IC papaverine (8-12mg). Adenosine was then infused in various doses either as IC bolus, IC infusion or IV infusion; the CBFs were measured and compared to the maximum CBF following papaverine.

Dose dependent increases in CBF were observed with adenosine over the range of doses used. Intravenous adenosine compares reasonably to IC papaverine and adenosine at 140mcg/kg/min produces a CBF response in 85% of patients equivalent to the maximum papaverine response. Lesser infusion rates of adenosine resulted in widely fluctuating CBF. All dose levels were well tolerated suggesting that an IV infusion of adenosine at 140µg/kg/min was an optimum dose to achieve a maximum increase of CBF. The effect was maximum 85 secs after starting the infusion. Heart rate was increased (mean 24bpm) and MAP reduced (mean 6mm Hg) at this dose.

Study [redacted], a double blind randomised cross over study in 20 male volunteers, compared adenosine IV infusion to exercise with respect to thallium-201 distribution kinetics. The results showed that both cardiac and extra cardiac thallium-201 uptake were significantly higher for adenosine compared to exercise. This would confirm the ability of IV adenosine to facilitate the uptake of thallium-201 in a similar way to exercise. The increased extra-cardiac uptake does not interfere with image interpretation.

The same study report [redacted]) includes a comparison of the effects of IV adenosine (15 mins at tolerated dose - max 140µg/kg/min) to dypyridamole 300mg orally on their ability to display a thallium perfusion defect in 15 patients with angiographically documented coronary disease.

With adenosine a defect was displayed in all 15 patients but only in 12 patients following dypyridamole.

7. CLINICAL EFFICACY

The clinical support for Adenoscan includes two pivotal studies (n=319) of identical design, three supportive studies (n=59), and reference to published experience with adenosine (n=498).

The pivotal studies [redacted] have been reported separately but the clinical expert decided to combine the results of both studies because the differences only related the method of image analysing.

Both were multicentre, cross over, fixed dose, with image analysis blinded, and compared the effects of Adenoscan or exercise in patients with angiographically confirmed coronary anatomy or normal volunteers on thallium 201 radionuclide myocardial perfusion imaging. Exercise was conducted to usual end points (max. HR, ST depression etc.) with T.201 injected 1 min before completion. Adenosine was administered at a dose of 140µg/kg/min for 6 mins; T 201 was injected after 3 mins. Dose and duration of adenosine infusion were based on study C-3 and published literature. This choice appears appropriate.

Study [redacted] was conducted in 93 patients and 55 volunteers: all completed but only 134 had interpretable scans for both exercise and adenosine. Concordance between the two, calculated blind, was 88.8% for detection of a perfusion defect (Global Score) and 90.3-94.8% for various regional perfusion scores. Disagreement tended towards cases where exercise indicated normal findings and adenosine abnormal.

Study [redacted] included 120 patients and 5 volunteers: all completed but only 163 had interpretable scans for both exercise and adenosine. Results were similar to the pervious study. Concordance between adenosine and exercise for Global scores was 82.8% and for regional perfusion 87.1-91.4%. Disagreements between the measures were even.

These are two well conducted studies with good statistical analyses. Overall concordance was 86% for detection of a perfusion defect and 84 to 93% for detection of regional hypoperfusion. It seems justifiable to consider the results together (Clinical Expert Report) and the total patients or volunteers studied ie. 297 provide adequate power for the conclusions.

Confirmation of these results is contained in the supportive studies and, more importantly, in the publications cited. These comprise well conducted studies (although open) published in respected peer reviewed cardiological journals.

Use of adenosine with imaging techniques using isotopes other than thallium 201 is also considered. Data from published studies as well as from a large ongoing safety study indicate that apparently useful diagnostic information is being obtained with other isotopes such as Technetium-99, Nitrogen-13, rubidium-82 and others.

8. SAFETY

The safety of Adenoscan is considered separately (rightly so) to that of Adenocor since dosage is higher and the patient population is different.

The database for the safety analyses are:

1. From completed clinical studies n=687
2. From a large ongoing US safety study n=14074
3. From published data.

The data from completed clinical studies allows the best evaluation of adverse events associated with adenosine infusion. Most subjects (n=561:82%) were patients with significant cardiovascular disease history with mean age of about 50-65 years. All subjects received 140μg/kg/min x 6 minutes: some subjects also received lower infusion rates, or IC infusions or IC papaverine, or oral dypyridamole.

Adverse events were frequent (80%) and consistent with the pharmacological actions of adenosine. Flushing, chest pain or pressure, and dyspnoea were so common as to be expected as normal. A wide variety of other events are reported. Overall, events were usually mild or moderate, severe in only 6%; duration very short, disappearing within minutes of cessation. Dose reduction was needed in 1.3%, premature termination in 1.5%, and reversal with theophylline in 1.5%.

AV block was seen in 23 patients, all but one resolved spontaneously, the remaining case needed the infusion terminated.

The ongoing US safety study is fully reported up to May 1993 at which point 14074 patients were enrolled. The study will be discontinued when NDA is approved. This is an open label

study to allow the use of adenosine in patients who are unable to exercise and who need cardiac imaging.

The profile of adverse events reported was similar to those observed in the clinical studies No patients were withdrawn, approximately 10% required early discontinuation of the infusion. The incidence of AV block at 7.2% was higher than previously reported but only 1.6% need dose adjustment, 0.6% terminated and 0.4% needed theophylline.

Serious adverse events have been reported in 10 patients which included 3 deaths. The non fatal events resolved with treatment (bronchospasm, VT, VT/VF). The deaths were similar in that all died of cardiac arrest during (53yr M) or after (20mins 66yr F; 4 hours 77yr M) adenosine infusion. All three had previous significant history of heart disease.

A 24hr safety profile in a 933 patient subset did not reveal any significant differences to the main database.

Little information is provided on the possibility of any interactions. Patients were on a wide variety of cardioactive and other medications but the only reference is a remark that 'there was no correlation between concomitant medications and adverse experiences in any of the drug classes examined'.

9. EXPERT REPORT

There is a well presented and well argued Clinical Expert Report from a [redacted] concludes that Adenoscan is safe and effective when used in accordance with the SPC.

10. DATA SHEET

This was considered satisfactory.

11. SPC

This was considered satisfactory.

12. PIL

This was considered satisfactory.

13. LABELLING

This was considered satisfactory.

14. MLA 201

This was considered satisfactory.

15. DISCUSSION

This is a well presented and argued application. The clinical data provided are adequate to show efficacy. Comparative safety against exercise testing has not been provided, although the pivotal studies were comparisons of adenosine and exercise. The safety profile of adenosine seems acceptable and the contra indications (AV block,asthma, S A disease) and precautions are appropriate.

The company is requesting the use of adenosine "as an alternative to exercise" but have not justified an improved risk / benefit ratio for adenosine over exercise. The clinical trial reports for both pivotal studies conclude that "adenosine will be particularly useful in patients unable to exercise adequately....." The clinical expert is careful not to express an opinion, one way or the other.

If the company cannot justify an improved risk / benefit ratio for adenosine the indications should be rephrased to reflect that its use should be restricted to patients unable to exercise adequately.

16. RECOMMENDATION

Subject to a satisfactory response to S44 points a product licence may be granted.

[redacted]

SENIOR MEDICAL OFFICER
10 November 1994

S44 POINTS
ADENOSCAN -PL 11723/0086

1. More information should be provided on the potential for interaction of adenosine with concomitant medications commonly used in the target patient population.

2. Provide an update of study [redacted] for deaths or severe adverse events.

3. Justify omission of severe bradycardia from side effects section of product literature since it is included for Adenocor.

Indication for Use

4. The use of adenosine "as an alternative to exercise" must be justified by demonstration of an improved risk / benefit ratio of adenosine to exercise.

5. It is noted that both pivotal clinical trials [redacted] conclude the study reports with the words "adenosine will be particularly useful in patients unable to exercise adequately...."

6. The indication for use of Adenoscan should be rephrased to reflect this statement or the company should provide justification for their own recommendation.
7. 36months. Only 6 months data is available, but this is supported by stability data for Adenocor.

8. In view of results for pH obtained in the stability studies, the finished product specification should be amended to include a suitable check limit for pH. (amended MLA 201 P. 8 required).

9. Confirmation that the batch size of Adenosine used in the stability studies was only 1200ml. should be provided.

10. Additional stability data for batches of suitable size should be provided in support of the proposed shelf-life, or consideration given to reducing the shelf-life at this stage.

11. The vial label should be amended to include a statement to the effect that any solution remaining after use should be discarded.

12. The Patient Information Leaflet should be amended to include the correct name and address of the manufacturer as given on MLA 201 P.11.