GLYCERYL TRINITRATE SPRAY 400 MICROGRAMS PER METERED DOSE SUBLINGUAL SPRAY
PL 16431/0023

UKPAR

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LAY SUMMARY

The MHRA granted Ayrton Saunders Limited a Marketing Authorisation for the medicinal product Glyceryl Trinitrate Spray 400 micrograms per metered dose sublingual spray (PL 16431/0023) on 11th September 2007. This pharmacy-only medicine (P) is used for rapid relief from an angina attack, and can also be used to prevent an anticipated attack.

The active ingredient, glyceryl trinitrate, acts by relaxing the muscle walls of the blood vessels and reduces the workload of the heart.

This application is identical to a previously granted application for Glyceryl Trinitrate Spray 400 micrograms per metered dose sublingual spray (PL 16431/0019) granted to the same Marketing Authorisation Holder on 21st November 2002. The original product was granted to Bioglan Laboratories Limited (PL 00041/0021) on the 14th June 1991.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Glyceryl Trinitrate Spray 400 micrograms per metered dose sublingual spray outweigh the risks; hence a Marketing Authorisation has been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Glyceryl Trinitrate Spray 400 micrograms per metered dose sublingual spray (PL 16431/0023) to Ayrton Saunders Limited on 11th September 2007. The product is a pharmacy-only medicine.

The application was submitted as a simple abridged application according to Article 10c of Directive 2001/83/EC, cross-referring to Glyceryl Trinitrate Spray 400 micrograms per metered dose sublingual spray (PL 16431/0019) approved on 21st November 2002.

No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) has been generated for it.

The product contains the active ingredient glyceryl trinitrate which acts on vascular smooth muscles to produce arterial and venous vasodilatation. The vasodilatation results in a reduction of venous return and an improvement in myocardial perfusion with the result of a reduction in the work performed by the heart and hence reduced oxygen demand.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 16431/0023
PROPRIETARY NAME: Glyceryl Trinitrate Spray 400 mircograms per metered dose sublingual spray
ACTIVE(S): Glyceryl Trinitrate
COMPANY NAME: Ayrton Saunders Limited
E.C. ARTICLE: Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC
LEGAL STATUS: P

1. INTRODUCTION

This is a simple, informed consent application for Glyceryl Trinitrate Spray 400 micrograms per metered dose sublingual spray submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Ayrton Saunders Limited, Peninsular Business Park, Reeds Lane, Moreton, Wirral, Merseyside, CH46 1DW, UK.

The application cross-refers to Glyceryl Trinitrate Spray 400 micrograms per metered dose sublingual spray (PL 16431/0019), approved on 21st November 2002 to the same marketing authorisation holder. The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the product is Glyceryl Trinitrate Spray 400 mircograms per metered dose sublingual spray. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains glyceryl trinitrate equivalent to 400µg per metered dose. It is to be stored in a pressurised aluminium container fitted with a metered valve. The proposed shelf-life (24 months) and storage conditions ("Store below 25^{o}C. Do not refrigerate or freeze. Do not expose to temperatures higher than 50^{o}C. Do not pierce the canister") are consistent with the details registered for the cross-reference product.

2.3 Legal status

On approval, the products will not be subject to a medical prescription, but will be supplied through pharmacies only.

2.4 Marketing authorisation holder/Contact Persons/Company

Peninsular Business Park, Reeds Lane, Moreton, Wirral, Merseyside, CH46 1DW, UK.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

2.9 Drug substance specification
There are differences between the proposed drug substance specification and the drug substance specification registered for the cross-reference product. Specifications for inorganic ions and GTN assay are broader than the limits registered for the cross reference product (but comply with the Ph.Eur. drug substance monograph).

2.10 TSE Compliance
There are no materials of animal origin in the product.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summary is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

Carton
The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the application are acceptable. A Marketing Authorisation should be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Glyceryl trinitrate is a well known drug and has been used for many years to relieve the pain caused by an angina attack. This application is identical to previously granted application for Glyceryl Trinitrate Spray 400 micrograms per metered dose sublingual spray (PL 16431/0019) granted to the same Marketing Authorisation Holder.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product which, in turn, has been shown to be interchangeable with the innovator product. Extensive clinical experience with glyceryl trinitrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 6th May 2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 2nd June 2005.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 25th October 2005, 9th November 2006, 16th January 2007, and 6th July 2007
4	The applicant responded to the MHRA's requests, providing further information on 21st November 2005, 5th December 2006, 13th June 2007 and 4th September 2007.
5	The application was determined on 11th September 2007

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Glyceryl Trinitrate Spray
400 micrograms per metered dose sublingual spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Glyceryl trinitrate: 400 micrograms per metered dose
(One metered dose with 8.8mg solution contains 400 micrograms glyceryl trinitrate)

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Metered dose sublingual spray solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of acute angina pectoris
Prevention of inducible angina (e.g. physical effort, emotional stress, exposure to cold)

4.2 Posology and method of administration
Route of administration: sublingual

Adults including the elderly
At the onset of an attack, one or two metered doses (400 to 800 micrograms glyceryl trinitrate) to be sprayed under the tongue for the relief of anginal pain while breath is held. No more than three doses are recommended at any one time.

For the prevention of inducible angina (e.g. physical effort, emotional stress, exposure to cold), one or two 400 microgram metered doses sprayed under the tongue within 2 – 3 minutes of the event starting.

Children
Glyceryl Trinitrate Spray is not recommended for children

Administration
During application the patient should rest, ideally in the sitting position. The canister should be held vertically with the valve head uppermost and the spray orifice as close to the mouth as possible. The dose should be sprayed under the tongue and the mouth should be closed immediately after each dose. The spray should not be inhaled. Patients should be instructed to familiarise themselves with the position of the spray orifice, which can be identified by the finger rest on top of the valve, in order to facilitate orientation, for administration at night.

4.3 Contraindications

Hypersensitivity to nitrates. Severe hypotension (systolic blood pressure lower than 90mm Hg). Hypotensive shock, severe anaemia, constrictive pericarditis, extreme bradycardia, Glucose-6-phosphate-dehydrogenase-deficiency, cerebral haemorrhage and brain trauma, aortic and / or mitral stenosis and angina caused by hypertrophic obstructive cardiomyopathy. Circulatory collapse, cardiogenic shock and toxic pulmonary oedema.

Sildenafil has been shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitrates or nitrate oxide donors is therefore contra-indicated.

4.4 Special warnings and precautions for use

Tolerance to this drug and cross-tolerance to other nitrates may occur.

Glyceryl Trinitrate Spray should be administered with particular caution in:

- Pericardial tamponade
- Low filling pressures (e.g. acute myocardial infarction, left ventricular failure)
- Tendency to dysregulation of orthostatic blood pressure
- Diseases accompanied by an increase in intracranial pressure (so far further pressure increase has been observed solely in high doses of glyceryl trinitrate).

Alcohol should be avoided because of the hypotensive effect. Medical controls of he intraocular pressure of glaucoma patients are advisable.

Particular caution should also be exercised when using Glyceryl Trinitrate Spray in patients with volume depletion from diuretic therapy, severe hepatic or renal impairment and hypothyroidism.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol may potentiate the hypotensive effect. Vasodilators, antihypertensives, β-blockers, calcium antagonists, neuroleptics, tricyclic antidepressants and diuretics can increase nitrate-induced hypotension.

The hypotensive effects of nitrates are potentiated by the concurrent administration of sildenafil.

The bioavailability of dihydroergotamine may be increased by concomitant use of Glyceryl Trinitrate Spray, which can result in vasoconstriction since dihydroergotamine can antagonise the effects of nitroglycerin. The concomitant administration of Glyceryl Trinitrate Spray and heparin can reduce the antithrombotic effect of heparin. Regular monitoring of coagulation parameters and adjustment of the heparin dose may be necessary.

In patients pre-treated with organic nitrates a higher dose of glyceryl trinitrate may be necessary to achieve the desired haemodynamic effect.

4.6 Pregnancy and lactation

The safety of glyceryl trinitrate in human pregnancy, especially during the first trimester has not been established. It is not known whether glyceryl trinitrate is excreted into human breast milk. Glyceryl Trinitrate Spray should be used only

after weighing the benefit for the mother against possible risks for the child. Nursing should be discontinued during treatment with this product.

4.7 Effects on ability to drive and use machines

The ability to react may be diminished because of the side effects or interactions due to the nitrates. This effect is potentiated by alcohol consumption. Therefore, driving and / or using machines should be avoided during treatment with Glyceryl Trinitrate Spray.

4.8 Undesirable effects

Frequent headache, occasional postural hypotension, facial flushing, vertigo, dizziness, weakness, nausea, tachycardia and paradoxical bradycardia have been reported.

Allergic skin reactions may occasionally occur. There have been reports of tongue blistering.

Rarely collapse states with bradycardia and syncope, a severe fall in blood pressure accompanied by an enhancement of the anginal symptoms, or exfoliative dermatitis may occur. Tolerance development and the occurrence of crossed tolerance of other nitro compounds have been found in chronic, continuous treatment using high doses. To avoid a decrease in efficacy or a loss of efficacy, high continuous doses should be avoided.

Use of Glyceryl Trinitrate Spray may give rise to transient hypoxaemia and, in patients with coronary heart disease, ischaemia as a result of a relative redistribution of the bloodstream, which is to hypoventilated alveolar areas.

4.9 Overdose

Signs and symptoms

Flushing, severe headache, vertigo, tachycardia, a feeling of suffocation, hypotension, fainting and rarely cyanosis and methaemoglobinaemia may occur. In a few patients, there may be a reaction comparable to shock with nausea, vomiting, weakness, sweating and syncope.

Treatment

Recovery often occurs without special treatment. Hypotension may be corrected by elevation of the legs to promote venous return. Methaemoglobinaemia should be treated by intravenous methylthioninium chloride and / or toluidine blue. Symptomatic treatment should be given for respiratory and circulatory defects in more serious cases.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-Code: CO1DAO2

Glyceryl trinitrate acts on vascular smooth muscles to produce arterial and venous vasodilatation. The vasodilatation results in a reduction of venous return and an

improvement in myocardial perfusion with the result of a reduction in the work performed by the heart and hence reduced oxygen demand.

5.2 Pharmacokinetic properties

Glyceryl trinitrate is rapidly absorbed through the buccal and sublingual mucosa, and in man, peak concentrations in plasma are observed within four minutes of sublingual administration.

The absolute bioavailability after sublingual administration is approximately 39%. After sublingual administration the plasma levels have shown a wide range of intra and inter individual variability.

The compound is extensively metabolised by liver enzymes and has a plasma half-life of 1 – 3 minutes. The principal mechanism of metabolism involves denitration.

5.3 Preclinical safety data

Reproductive Toxicity

Animal studies conducted with various routes of administration have not shown teratogenicity, other embryotoxic effects or impairment of fertility with dosages including parental toxicity. Data from in-vitro mutagenicity testing as well as from studies in animals indicate that glyceryl trinitrate will not exert mutagenic or carcinogenic effects under conditions of clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Peppermint Oil
Propellant 1,1,1,2-tetrafluoroethane (HFC 134A)
Ethanol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Two years

6.4 Special precautions for storage

Store below 25ºC.
Do not refrigerate or freeze.
The canister contains a pressurised liquid. Do not expose to temperatures higher than 50ºC. Do not pierce canister.

6.5 Nature and contents of container

Internally lacquered monobloc aluminium pressurised container, sealed with a metered spray valve.

The product is presented in packs with one metered dose spray.

One metered dose spray (= one aluminium container) contains 1760.0mg of solution (according to 11400.0mg of solution and propellant) providing 200 single metered doses.

6.6 Special precautions for disposal

Glyceryl Trinitrate Spray is a pressurised container, which must not be pierced or burnt even after use. It should not be sprayed at a naked flame or any incandescent material. Patients, especially those who smoke, should be warned not to use Glyceryl Trinitrate Spray near a naked flame.

7 MARKETING AUTHORISATION HOLDER

Ayrton Saunders Ltd.,
Peninsular Business Park,
Reeds Lane, Moreton,
Wirral, Merseyside,
CH46 1DW,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL16431/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/09/2007

10 DATE OF REVISION OF THE TEXT

11/09/2007

GLYCERYL TRINITRATE SPRAY 400 MICROGRAMS PER METERED DOSE SUBLINGUAL SPRAY
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PATIENT INFORMATION LEAFLET

WHAT YOU SHOULD KNOW ABOUT

Glyceryl Trinitrate Spray
400 micrograms per metered dose sublingual spray

Please read this carefully before you start to use this medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

WHAT IS IN YOUR MEDICINE?

Your medicine is called Glyceryl Trinitrate Spray, 400 micrograms per metered dose sublingual spray, but it will be referred to as Glyceryl Trinitrate Spray throughout this leaflet.
It is a metered aerosol which delivers 400 micrograms of glyceryl trinitrate, the active ingredient, each time the button is pressed.
It contains the following inactive ingredients: peppermint oil, 1,1,1,2 tetrafluoethane, ethanol. This product contains small amounts of ethanol (alcohol), less than 100mg per spray. Each aerosol can contains 200 doses.
Glyceryl trinitrate is one of a group of medicines called nitrates which relax the muscle walls of the blood vessels and reduce the workload of the heart.

Manufactured by:	Product Licence Holder:
Pharmasol Limited,	Ayrton Saunders Ltd
North Way	Reeds Lane
Andover	Moreton
Hants	Wirral
SP10 5AZ, UK.	CH46 1DW, UK.

WHAT IS YOUR MEDICINE FOR?

You may use Glyceryl Trinitrate Spray to relieve the pain of an angina attack as soon as it has started or to prevent it starting by using immediately before events which may set off your angina, for instance physical effort, emotional stress or exposure to cold.

BEFORE USING YOUR MEDICINE

If you can answer yes to any of the following questions, do not use Glyceryl Trinitrate Spray without first talking to your doctor:

1. Are you hypersensitive to nitrates or any of the other ingredients of Glyceryl Trinitrate Spray?
2. Are you pregnant or likely to become so?
3. Are you breast-feeding your baby?
4. Do you have a very low blood pressure or heart rate, severe anaemia, abnormality of the heart valves or heart muscle, head injury, bleeding from the brain or fluid on the lungs?
5. Are you taking any medication, particularly heart, blood pressure or water tablets or Viagra? If Viagra (sildenafil - for male erectile dysfunction) is used by patients taking nitrate preparations such as Glyceryl Trinitrate Spray, a severe and possibly dangerous fall in blood pressure can occur. This would result in collapse, unconsciousness and could be fatal. You should not take Viagra whilst on Glyceryl Trinitrate Spray.

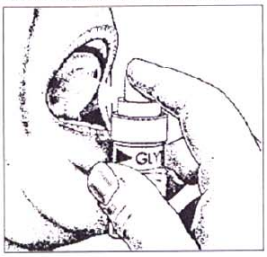
Continued use of nitrates may result in reduced effectiveness.

You may wish to use Glyceryl Trinitrate Spray urgently or in the dark, so if you have never used it before, practice spraying a few puffs into the air.

Never use Glyceryl Trinitrate Spray near a naked flame, e.g. a cigarette.
Glyceryl Trinitrate Spray should not be taken with alcohol.
Driving or using machines should be avoided during use of Glyceryl Trinitrate Spray.

USING YOUR MEDICINE

Always check the label for directions on how to take your medicine. Your pharmacist or doctor will help if you are not sure.
If possible, it is recommended that you sit down to use your medicine.
Remove the cap. Hold the canister upright with forefinger on top of the white button.
There is no need to shake the canister.



Open your mouth and bring the Glyceryl Trinitrate Spray nozzle as close as possible, aiming it under your tongue.

Press the button firmly, directing the spray under your tongue while holding your breath. Keep the button held down until all the dose has been released. Close your mouth immediately but do not inhale the spray.

If necessary, repeat for a second time following the steps above. No more than three doses are recommended at one time.

Always replace the cap after use.

If you use Glyceryl Trinitrate Spray during an attack, sit down and rest until the pain disappears.

AFTER USING YOUR MEDICINE

Glyceryl Trinitrate Spray can frequently cause headaches. Other side effects that may be encountered are facial flushing, faintness, abnormal heart rate, dizziness and nausea. In addition, allergic skin rashes may occasionally occur. Rarely, patients have collapsed as a result of a great fall in blood pressure. There have been reports of tongue blistering. You may only need to consult your doctor if these symptoms become troublesome. These symptoms may be made worse if you have been drinking alcohol or are taking prescribed medicine for high blood pressure.
If you experience any other ill effects, tell your doctor or pharmacist immediately and ask if you should continue with your medication. If you find that your medication is becoming less effective, discuss this with your doctor or pharmacist as increasing the dose would be of no added value and could be dangerous.

KEEPING YOUR MEDICINE SAFE

Store below 25ºC. Do not refrigerate or freeze.
Do not use any medicine after the expiry date stated on the packaging.

Keep out of reach and sight of children.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50ºC. Do not pierce the canister.
Make sure you have a Glyceryl Trinitrate Spray with you at all times.
make sure you get a new one before the old one runs out. Ideally keep a spare handy.
REMEMBER this medicine is for you. Never give it to others. It may harm them even if their symptoms are the same as yours.

Date of preparation or last review: July 2007 MP00559 v0707

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LABELLING

CARTON