ADRENALINE (EPINEPHRINE) 1 IN 1000 SOLUTION FOR INJECTION BP

PL 12064/0122

UKPAR

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ADRENALINE (EPINEPHRINE) 1 IN 1000 SOLUTION FOR INJECTION BP

PL 12064/0122

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Aurum Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Adrenaline (Epinephrine) 1 in 1000 solution for Injection BP (PL 12064/0122). This prescription only medicine (POM) suppresses the immune system and is used to treat anaphylaxis (a severe and rapid allergic reaction).

Adrenaline (Epinephrine) 1 in 1000 solution for Injection BP contains the active ingredient adrenaline acid tartrate, a natural antidote to the chemicals released during anaphylaxis.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Adrenaline (Epinephrine) 1 in 1000 solution for Injection BP outweigh the risks, hence a Marketing Authorisation has been granted.

ADRENALINE (EPINEPHRINE) 1 IN 1000 SOLUTION FOR INJECTION BP

PL 12064/0122

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisation for the medicinal product Adrenaline (Epinephrine) 1 in 1000 solution for Injection BP (PL 12064/0122) to Aurum Pharmaceuticals Limited on 13 June 2006. This product is a POM.

The application was submitted as an abridged informed consent application according to Article 10c of EC Directive 2001/83.

The cross reference product is Adrenaline (Epinephrine) injection BP 1:1000 for anaphylaxis, 1.000mg/ml solution for injection (PL 12064/0058), held by Aurum Pharmaceuticals and granted 29 July 1999.

No new data was submitted, nor was it necessary for this simple application, as the data is 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) was generated for it.

PHARMACEUTICAL ASSESSMENT REPORT

INTRODUCTION

This is an abridged application made under Article 10c of EC Directive 2001/83, an informed consent application. The authorised product is PL 12064/0058 (Adrenaline (Epinephrine) injection BP 1:1000 for anaphylaxis, 1.000mg/ml solution for injection).

The licence for the cross reference product is held by Aurum Pharmaceuticals, granted 29 July 1999. The application for Adrenaline (Epinephrine) 1 in 1000 solution for Injection BP (PL 12064/0122) was submitted March 2006.

A letter of consent has not been supplied by Aurum for cross reference to PL 12064/0058 in conjunction with this application. This is acceptable as it is the same marketing authorisation holder.

The finished product is being manufactured by the same company that manufactures the cross reference product and is also listed with functions of assembly, distribution, batch release and quality control. A manufacturers licence has been provided for this site and is valid until August 2010. A manufacturing and wholesale authorisation has been provided for the product manufacturer from the relevant authorities dated July 2005. A GMP certificate has also been provided from the authorities dated May 2005. The sites included are in compliance with the cross reference licence.

A letter has not been provided to confirm manufacture, as this application is from the marketing authorisation holder of the cross reference licence this is acceptable.

The active ingredient supplier is in compliance with the cross reference licence.
The certificate of suitability has been provided, granted January 2006. The certificate authorises use by Aurum Pharmaceuticals.

QUALITY OVERALL SUMMARY

Satisfactory statements and summaries have been provided.

PRODUCT LITERATURE

1. Summary of Product Characteristics

The Summary of Product Characteristics (SPC) is satisfactory.

2. Label

All labelling is satisfactory.

3. PIL

The Patient Information Leaflet (PIL) is satisfactory.

4. MAA

This Marketing Authorisation Application is acceptable.

RECOMMENDATION

Grant of a Marketing Authorisation is acceptable.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none is 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

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. The risk benefit ratio is considered to be positive.

ADRENALINE (EPINEPHRINE) 1 IN 1000 SOLUTION FOR INJECTION BP

PL 12064/0122

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 6 March 2006
2	Following assessment of the application the MHRA requested further information relating to the quality dossier on 16 March 2006
3	The applicant responded to the MHRA's requests, providing further information on 25 April 2006
4	The application was determined on 13 June 2006

SUMMARY OF PRODUCT CHARACTERISTICS

Product Summary for Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP

1 NAME OF THE MEDICINAL PRODUCT

Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Adrenaline (Epinephrine) (as acid tartrate) 1mg per ml.
Each 1ml pre-filled syringe contains 1mg Adrenaline (Epinephrine) (as acid tartrate).
Also contains Sodium Chloride and Sodium Metabisulphite.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.
Clear colourless solution, practically free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Anaphylaxis or Acute Allergy (Angioedema)

4.2 Posology and method of administration

Anaphylaxis or Acute Allergy (Angioedema)

Adults and children over 12 years

A dose of 0.5 - 1.0 ml (0.5 - 1.0ml of *Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP*) given by intramuscular injection, repeated every ten minutes, according to blood pressure and pulse, until improvement occurs.

When the patient is severely ill and there is real doubt about adequacy of the circulation and absorption from the intramuscular injection site, adrenaline /epinephrine may be given by **slow** intravenous injection in a dose of 500 micrograms given at a rate of 100 micrograms per minute using a 1:10,000 dilution of adrenaline/epinephrine (i.e. a 1:10ml dilution of the contents of the syringe)

Children over 12 who are prepubertal or small should be given a half dose (i.e. 250 micrograms)

Children under 12 years

The following table shows the volume of *Adrenaline (Epinephrine) 1 in 1000*

Solution for Injection BP (1mg in 1ml) for intramuscular injection.

AGE	VOLUME OF *ADRENALINE (EPINEPHRINE) 1 in 1000 SOLUTION FOR INJECTION BP*
< 6 months	50 micrograms IM (0.05 ml, absolute accuracy not essential)
> 6 months - 6 years	120 micrograms IM (0.12 ml)*
6-12 years	250 micrograms IM (0.25 ml)*

* *Suitable for robust children in these age groups; for underweight children use half these doses*

When the child is severely ill and there is real doubt about adequacy of the circulation and absorption from the intramuscular injection site, adrenaline /epinephrine may be given by **slow** intravenous injection in a dose of 10 micrograms/ kg over several minutes using a 1:10,000 dilution of adrenaline /epinephrine (i.e. a 1:10ml dilution of the contents of the syringe). Constant vigilance is needed to ensure that the correct strength is used.

4.3 Contraindications

Adrenaline/epinephrine is contraindicated in patients with shock (other than anaphylactic shock), organic heart disease, or cardiac dilatation, as well as most patients with arrhythmias, organic brain damage, or cerebral arteriosclerosis. Adrenaline/epinephrine injection is contraindicated in patients with narrow angle glaucoma. Adrenaline/epinephrine is contraindicated for use during general anaesthesia with chloroform, trichloroethylene, or cyclopropane, and should be used cautiously, it at all, with other halogenated hydrocarbon anaesthetics. Adrenaline/epinephrine is contraindicated for use in fingers, toes, ears, nose or genitalia.

Adrenaline/epinephrine should not be used during the second stage of labour (see pregnancy and lactation).

4.4 Special warnings and precautions for use

IM injection of adrenaline/epinephrine into the buttocks should be avoided because of the risk of tissue necrosis. Prolonged use of adrenaline/epinephrine can result in severe metabolic acidosis because of elevated blood concentrations of lactic acid.

Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP contains less than 1mmol sodium (23mg) per pre-filled syringe, i.e. essentially 'sodium-free'.

Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP contains sodium metabisulphite that can cause allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic episodes, in certain susceptible individuals.

The presence of sodium metabisulphite in parenteral adrenaline/epinephrine and the possibility of allergic-type reactions should not deter use of the drug when indicated for the treatment of serious allergic reactions or for other emergency situations.

Care should be exercised in patients who suffer from diabetes mellitus, hypertension and hyperthyroidism.

4.5 Interaction with other medicinal products and other forms of interaction

- Sympathomimetic agents: Adrenaline/epinephrine should not be administered concomitantly with other sympathomimetic agents because of the possibility of additive effects and increased toxicity.
- Alpha and beta blocking agents: The cardiac and bronchodilating effects of adrenaline/epinephrine are antagonised by β-adrenergic blocking drugs such as propranolol, and the vasoconstriction and hypertension caused by high doses of adrenaline/epinephrine are antagonised by alpha-adrenergic blocking agents such as phentolamine.
- Because of their alpha-adrenergic blocking properties, ergot alkaloids can reverse the pressor response to adrenaline.
- General anaesthetics (see also contraindications) Administration of adrenaline/epinephrine in patients receiving cyclopropane or halogenated hydrocarbon general anaesthetics that increase cardiac irritability and seem to sensitise the myocardium to adrenaline/epinephrine may result in arrhythmias including ventricular premature contractions, tachycardia, or fibrillation.
- Prophylactic administration of lignocaine or prophylactic administration of propranolol 0.05 mg/kg may protect against ventricular irritability if adrenaline/epinephrine is used during anaesthesia with a halogenated hydrocarbon anaesthetic.

Other Drugs:

- Adrenaline/epinephrine should not be used in patients receiving high dosage of other drugs (e.g. cardiac glycosides) that can sensitise the heart to arrhythmias. Tricyclic antidepressants such as imipramine, some antihistamines (e.g. diphenhydramine) and thyroid hormones may potentiate the effects of adrenaline/epinephrine, especially on heart rhythm and rate. Although monoamine oxidase (MAO) is one of the enzymes responsible for adrenaline/epinephrine metabolism, MAO inhibitors do not markedly potentiate the effects of adrenaline/epinephrine.
- Phenothiazine: Adrenaline/epinephrine should not be used to counteract circulatory collapse or hypotension caused by phenothiazines: a reversal of adrenaline/epinephrine's pressor effects resulting in further lowering of blood pressure may occur.

- Insulin and other hypoglycaemic agents: Because adrenaline/epinephrine may cause hyperglycaemia, diabetic patients receiving adrenaline/epinephrine may require increased dosage of insulin or oral hypoglycaemic agents.
- Clonidine may increase the risk of hypertension.
- Dopexamine may enhance the action of adrenaline.
- Entacapone may enhance the action of adrenaline.
- Antipsychotics antagonise the hypertensive effect of sympathomimetics.
- Doxapram: Increased risk of hypertension when sympathomimetics are given with doxapram.
- Ergotamine and Methylsergide: There is an increased risk of ergotism if sympathomimetics are given with these drugs.
- Oxytocin: Concomitant use with adrenaline may increase the vasopressor effect and thus a risk of hypertension may develop. (see also Section 4.6)

4.6 Pregnancy and lactation

Adrenaline/epinephrine usually inhibits spontaneous or oxytocin induced contractions of the pregnant human uterus and may delay the second stage of labour. In dosage sufficient to reduce uterine contractions, the drug may cause a prolonged period of uterine atony with haemorrhage. If used during pregnancy, adrenaline/epinephrine may cause anoxia to the foetus.

For this reason parenteral adrenaline/epinephrine should not be used during the second stage of labour. Adrenaline/epinephrine should only be used during pregnancy if the potential benefits justify the possible risks to the foetus. Adrenaline /epinephrine is distributed into breast milk. Breast-feeding should therefore be avoided in mothers receiving Adrenaline/Epinephrine Injection.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

- Hyperglycaemia.
- Anxiety.
- Headache, nausea, vomiting, sweating, tremors, dizziness or restlessness.
- Adrenaline/epinephrine causes ECG changes including a decrease in T-wave amplitude in all leads in normal persons. (16) Disturbances of cardiac rhythm and rate may result in palpitation and tachycardia. Adrenaline/epinephrine can cause potentially fatal ventricular arrhythmias including fibrillation, especially in patients with organic heart disease or receiving other drugs that sensitise the heart to arrhythmias. Subarachnoid haemorrhage and hemiplegia have resulted from hypertension, even following subcutaneous administration of usual doses of adrenaline.
- Dyspnoea.

- Weakness. In patients with Parkinsonian syndrome, adrenaline/epinephrine increases rigidity and tremor.
- Coldness of the extremities may occur even with small doses of adrenaline /epinephrine. Repeated injections of adrenaline/epinephrine can cause necrosis as a result of vascular constriction at the injection site. Tissue necrosis may also occur in the extremities, kidneys and liver.

4.9 Overdose

After overdose or inadvertent IV administration of usual doses of adrenaline/epinephrine, systolic and diastolic blood pressure rise sharply; venous pressure also rises. Cerebrovascular or other haemorrhage and hemiplegia may result, especially in elderly patients. Because adrenaline /epinephrine is rapidly inactivated in the body, treatment of acute toxicity is mainly supportive.

The pressor effects of adrenaline/epinephrine may be counteracted by an immediate intravenous injection of a quick-acting alpha-adrenoceptor blocking agent, such as 5 - 10mg of phentolamine mesylate, followed by a beta-adrenoceptor blocking agent such as 2.5mg to 5mg of propranolol.

Adrenaline/epinephrine overdosage causes transient bradycardia followed by tachycardia and may cause other potentially fatal cardiac arrhythmias. Arrhythmias, if they occur, may be counteracted by propranolol injection. Kidney failure, metabolic acidosis and cold, white skin may also occur.
Pulmonary oedema may be caused by overdosage or extreme sensitivity to adrenaline.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: adrenergic and dopaminergic agents, adrenaline.

ATC code: C01CA24

Adrenaline/epinephrine is an active principle of the adrenal medulla which is used as a direct-acting sympathomimetic agent. Adrenaline/epinephrine has a somewhat more marked effect on beta-adrenoceptors than on alpha-adrenoceptors. In addition, its actions vary considerably according to the dose given, and the consequent reflex compensating responses of the body. Adrenaline/epinephrine produces marked and concentration-dependent increases in stroke volume, cardiac output and systemic vascular resistance when arterial plasma concentration is increased from 0.3 to 6nmol/l (0.055 to 1.1pg/l).

In practice, major effects of adrenaline/epinephrine include increased speed and force of cardiac contraction (with lower doses this causes increased systolic pressure yet reduced diastolic pressure since overall peripheral resistance is lowered, but with higher doses both systolic and diastolic pressure are increased as stimulation of peripheral alpha-receptors increases peripheral resistance); blood flow to skeletal

muscle is increased (reduced with higher doses); metabolic effects include increased glucose output as well as markedly increased oxygen consumption; blood flow in the kidneys, mucosa, and skin is reduced; there is little direct effect on cerebral blood flow.

5.2 Pharmacokinetic properties

Adrenaline/epinephrine acts rapidly following intramuscular ~~and subcutaneous~~ injection. Local vasoconstriction can slow absorption, but *is* hastened by massaging *the* injection site.

Adrenaline/epinephrine injected into the body, or released from the adrenal medulla is very rapidly inactivated by processes, which include uptake into adrenergic neurones, diffusion, and enzymatic degradation in the liver and body tissues.

Adrenaline/epinephrine is rapidly distributed into the heart, spleen, several glandular tissues and adrenergic nerves. It is approximately 50% bound to plasma proteins.

Endogenous plasma concentrations of adrenaline/epinephrine in normal subjects are in the range 30 to 160 ng/l.

The decline of plasma adrenaline/epinephrine following intravenous infusion has been reported to be biexponential with a mean clearance of 9.4 l/min (range 4.9-14.6 l/min). The half-lives of the fast and slow exponential phases are approximately 3 and 10 minutes respectively.

One of the enzymes responsible for the chemical inactivation of this exogenous or hormonal adrenaline/epinephrine is Catechol-O-methyltransferase (COMT), the other is monoamine oxidase (MAO).

In general:

The metabolites are excreted in the urine mainly as their glucuronide and ethereal sulphate conjugates. About 70-95% of an intravenous dose is excreted in the urine; of the excreted material, about 80% is excreted as O-methyl metabolites and 2% as catechol metabolites, and only 1% is excreted as unchanged drug.

Adrenaline/epinephrine is inactivated by the introduction of a methyl group by COMT. Thus the termination of the pharmacological response of adrenaline /epinephrine (and other catecholamines) is not only dependent on MAO. However, in adrenaline/epinephrine's role as a neurotransmitter, it is enzymatically regulated by MAO.

Adrenaline/epinephrine crosses the placenta to enter the foetal circulation.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber, which are additional to

that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Sodium Metabisulphite
Water for Injections
Dilute Hydrochloric Acid *(for pH adjustment)*

6.2 Incompatibilities

Adrenaline/epinephrine is rapidly denatured by oxidising agents and alkalis including sodium bicarbonate, halogens, nitrates, nitrites, and salts of iron, copper and zinc. Adrenaline/epinephrine may be mixed with 0.9% sodium chloride injection but is incompatible with 5% sodium chloride injection. The stability of adrenaline/epinephrine in 5% dextrose injection decreases when the pH is greater than 5.5.

6.3 Shelf life

12 months.

6.4 Special precautions for storage

Keep the pre-filled syringe in the outer carton.
Do not store above 25°C.
Do not freeze

6.5 Nature and contents of container

Type 1 Glass prefilled Syringe with needle in situ with rubber needle shield, rubber plunger (Type PH 701/50C).

6.6 Special precautions for disposal

Do not use if the contents of the syringe are discoloured. Do not use if the tamper evident seal is broken or the packaging is damaged. Use once and discard any remaining solution at the end of the session.

7 MARKETING AUTHORISATION HOLDER

Aurum Pharmaceuticals Ltd.
Bampton Road,
Harold Hill,
Romford,

Essex,
RM3 8UG.
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 12064/0122

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/06/2006

10 DATE OF REVISION OF THE TEXT

13/06/2006

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET C91193

Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP For Anaphylaxis (In a prefilled 1ml syringe with an attached needle)

Please read this leaflet carefully before you are given or use this injection.

- Keep this leaflet. You may need to read it again.
- The injection may be administered by a doctor/nurse or you may have been taught how to inject yourself.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP is a prefilled syringe containing the active substance Adrenaline (Epinephrine) (as acid tartrate) 1mg per ml. The other ingredients are Sodium Chloride, Sodium Metabisulphite and Water for Injections. Dilute Hydrochloric acid may be added to adjust the acidity.

Marketing Authorisation Holder:
Aurum Pharmaceuticals Ltd.
Bampton Rd, Romford, RM3 8UG.
United Kingdom

Manufacturer:
Federa SC
Avenue Jean Jaurèslaan 71,
Brussels B-1030. Belgium.

What is Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP and what is it used for

Each 1ml pre-filled syringe of Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP contains 1ml of a clear colourless solution, practically free from particles with Adrenaline (Epinephrine) (as acid tartrate) 1mg per ml. The injection is available as a single 1ml glass prefilled syringe fitted with a needle and contained in a carton.

Adrenaline belongs to a group of medicines used in the treatment of serious shock or collapse. This injection is used to treat shock produced by a severe allergic reaction.

Before you use Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP

Your doctor will be aware of the following information before they decided to give you this medicine.

Do not use Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP if:

- You are allergic to any of the ingredients in this injection.
- You are suffering from any heart disease.
- You are in shock (other than that caused by an acute life threatening reaction).
- You are suffering from brain damage or hardening of the arteries in the brain.
- You are suffering from glaucoma (increased pressure in the eye).
- You are undergoing or are about to undergo an operation under a general anaesthetic.
- You are in the second stage of labour.

Take special care with Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP if:

- You are suffering from high blood pressure.
- You are pregnant or breastfeeding.
- You are diabetic.
- You are taking antihistamines or tricyclic antidepressants.
- You are taking drugs to treat high blood pressure, heart conditions, or thyroid problems.
- You are taking ergot alkaloids (drugs used to treat migraine).

Please inform your doctor or pharmacist if you are taking or have taken any other medicine - even those not prescribed.

Adrenaline must not be administered into fingers, toes, ears, nose or genitalia.

Injection of adrenaline into the buttocks should be avoided because of the risk of tissue damage.

Prolonged use of adrenaline can result in increased levels of lactic acid in your or your child's blood.

Important information about some of the ingredients in this medication
Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP contains less than 1mmol sodium (23mg) per pre-filled syringe, i.e. essentially 'sodium-free'.

This product contains Sodium Metabisulphite which may cause allergic type reactions in some people. This may lead to breathing difficulties or collapse. People with a history of asthma or allergies are most likely to experience these problems.

How to use this Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP
If you have been taught to administer the injection yourself, you should follow the directions given by your doctor. If you have not been taught, your doctor, nurse or paramedic will administer adrenaline to you into a muscle (intramuscular).

In emergencies it may be necessary for a medically qualified person to administer an adrenaline solution slowly into a vein (intravenous). Your doctor will decide the correct dosage for you and when and how the injection should be administered.

*Adults and children over 12 years**
A dose of 0.5 - 1.0 mg (0.5 - 1.0ml of Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP) given by injection into the muscle (intramuscular). This may be repeated every ten minutes, according to your blood pressure and pulse, until an improvement occurs.

Children who are small or have not reached puberty should be given 250 micrograms (0.25ml).

Children under 12 years
The following table shows the volume of Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP (1mg in 1ml) for injection into the muscle (intramuscular).

AGE	VOLUME OF ADRENALINE (EPINEPHRINE) 1 in 1000 SOLUTION FOR INJECTION BP
< 6 months	50 micrograms IM (0.05ml, absolute accuracy not essential)
6 months – 6 years	120 micrograms IM (0.12ml)*
6 – 12 Years	250 micrograms IM (0.25ml)*

* For underweight children half doses should be given

If you have been given too much of this medication your doctor will take appropriate action. If you believe you have used too much of this medication seek immediate medical assistance.

Possible side effects
You may experience some of the following side effects: anxiety, difficulty in breathing, high blood sugar levels, restlessness, palpitations, irregular or faster heartbeat, tremors, weakness, dizziness, headache and coldness in the extremities. In patients with Parkinson's disease adrenaline may increase rigidity and tremors.

Adrenaline may cause changes in your heart tracing (ECG). It may cause high blood pressure which, if very high, may cause bleeding in the brain. This may lead to a stroke and loss of movement on one side of the body.
Repeated injection may cause tissue damage at the site of injection. Tissue damage may also occur in the extremities, kidneys and liver.

If any of the effects are troublesome or you notice any other effects please tell your doctor.

Storing Adrenaline (Epinephrine) 1 in 1000 Solution for Injection BP
Keep the pre-filled syringe in the outer carton. Do not store above 25°C. Do not freeze.
The person administering this injection must check that the expiry date on the labels has not been passed before administering the injection and the product must not be used if it has become discoloured. Use once and discard any remaining solution.
Keep out of the reach and sight of children.

Date of revision: March 2006
Licence number: PL12064/0122
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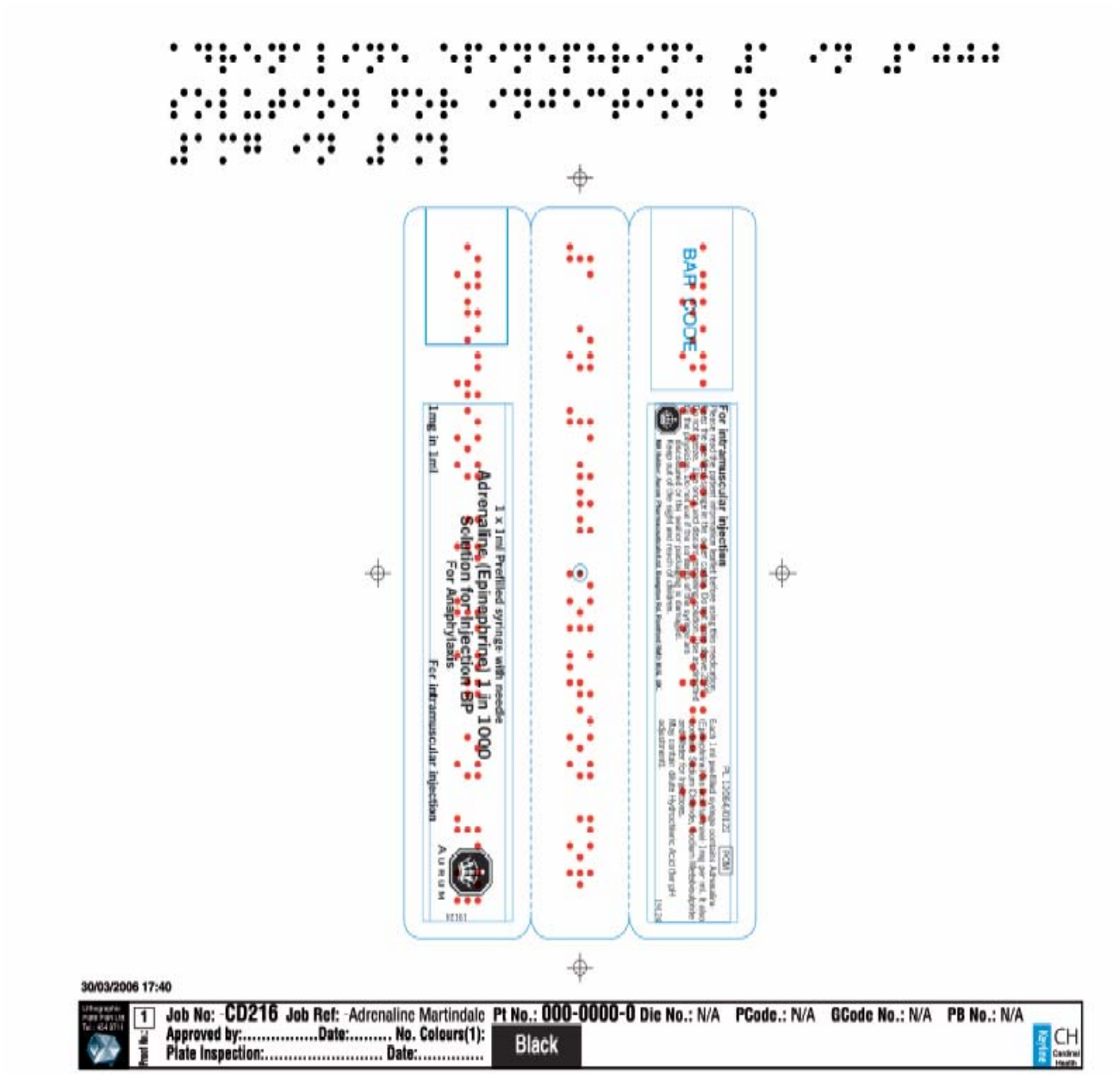
Aurum Pharmaceuticals Ltd.
Bampton Rd, Romford, RM3 8UG, UK.

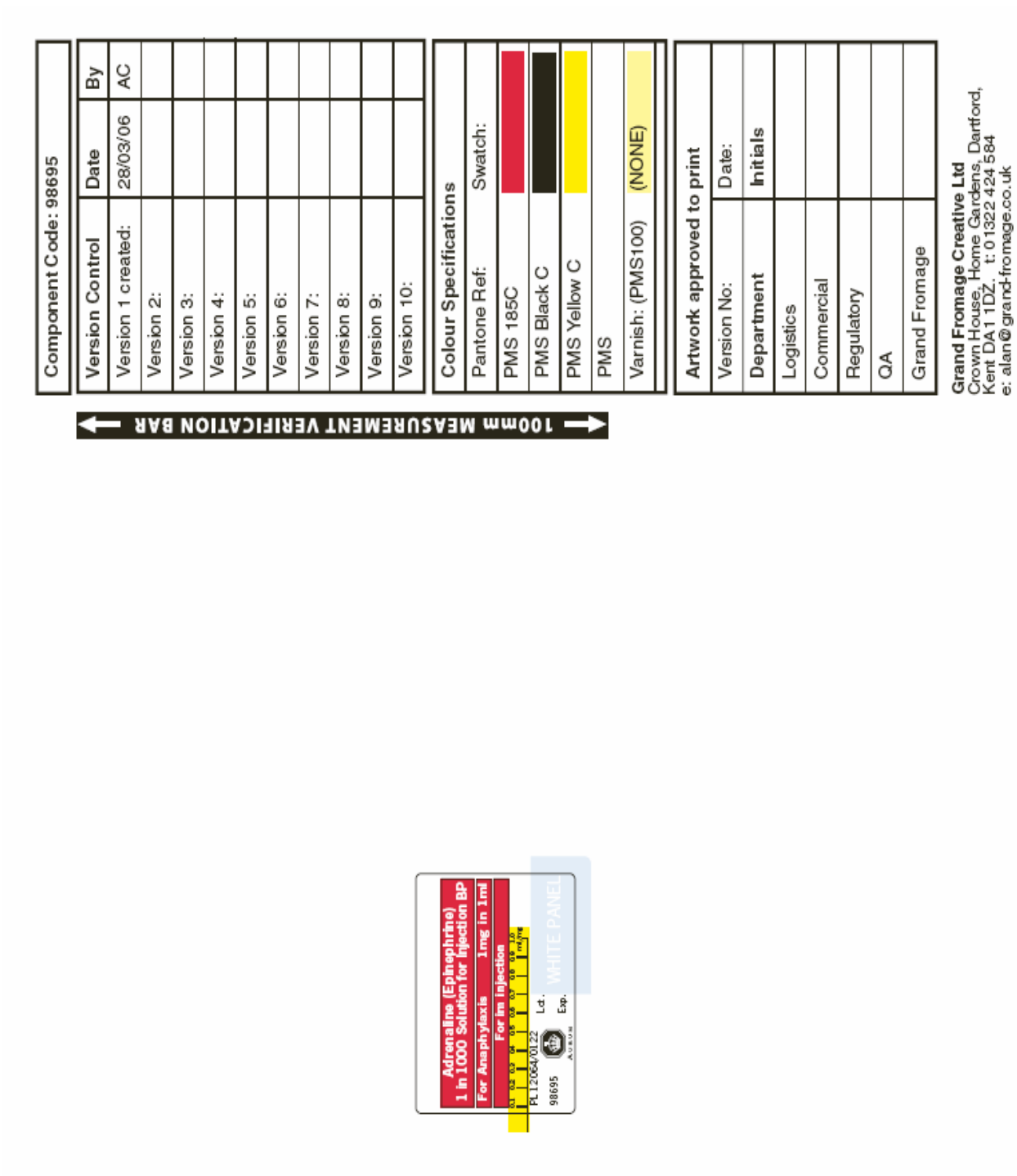
C91193

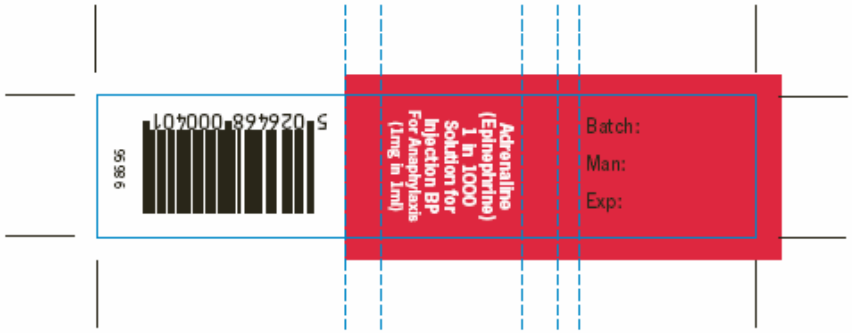
LABELLING

Box label:



Syringe label:





100mm MEASUREMENT VERIFICATION BAR

Component Code: 98696		
Version Control	**Date**	**By**
Version 1 created:	28/03/06	AC
Version 2:		
Version 3:		
Version 4:		
Version 5:		
Version 6:		
Version 7:		
Version 8:		
Version 9:		
Version 10:		

Colour Specifications	
Pantone Ref:	Swatch:
PMS 185 C	
PMS Black C	
PMS	
PMS	
Varnish: (PMS100)	(NONE)

Artwork approved to print	
Version No:	Date:
Department	**Initials**
Logistics	
Commercial	
Regulatory	
QA	
Grand Fromage	

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