VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

1. Adrenalin Bradex, 1 mg/ml, Solution for Injection is used to relieve bronchial spasm in acute attacks of asthma.

It may also be used to provide rapid relief of hypersensitivity reactions to drugs and other allergens, and in the emergency treatment of anaphylactic shock.

Asthma attack

Asthma is the most common chronic respiratory disease, affecting up to 10% of adults and 30% of children in the Western world. Despite advances in asthma management, acute exacerbations continue to occur and impose considerable morbidity on patients and constitute a major burden on health care resources. Early treatment of asthma exacerbations is the best strategy for management. The first successful treatment of acute, severe asthma with SC injections of ADR was noted 100 years ago, in 1903 in New York, by Bullowa and Kaplan, who reported on an extremely successful treatment of severe acute asthma with SC injections of ADR.

Hypersensitivity reactions and anaphylactic shock

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterized by rapidly developing, life-threatening problems involving the airway (pharyngeal or laryngeal oedema) and/or breathing (bronchospasm with tachypnoea) and/or circulation (hypotension and/or tachycardia). Foods, medications, insect stings, and allergen immunotherapy injections are the most common provoking factors for anaphylaxis, but any agent capable of producing a sudden degranulation of mast cells or basophils can induce anaphylaxis.

ADR is the first-line treatment in all cases of anaphylaxis. ADR should be administered as soon as possible once anaphylaxis is recognized, and the patient should be transported to the nearest emergency facility. Adrenaline is the most important drug for the treatment of an anaphylactic reaction.

2. Adrenalin Bradex, 1 mg/ml, Solution for Injection can be used for the treatment of cardiac arrest. Adrenalin Bradex, 1 mg/ml, Solution for Injection may be used in follow-up treatment in cardiopulmonary resuscitation.

Sudden unexpected cardiac arrest is a global challenge. Some deaths are preventable and some arrests can be treated successfully and result in a very good long-term outcome. In Europe and USA ischaemic heart disease is considered the main cause of sudden cardiac arres.

Historically, ADR has been used for the treatment of cardiac arrest for over 100 years. ADR is a powerful agonist at both α- and β-adrenergic receptors.

There is increasing recognition that systematic post-cardiac arrest care after restoration of spontaneous circulation can improve the likelihood of patient survival with good quality of life. Post- cardiac arrest care has significant potential to reduce early mortality caused by haemodynamic instability and later morbidity and mortality from multiorgan failure and brain injury.

VI. 2.2 Summary of treatment benefits

Adrenaline belongs to a class of drugs called sympathomimetic agent. Adrenaline may be used to rapidly relieve severe allergic reactions to drugs or other substances causing allergy. It may also be used in the emergency treatment of shock due to a severe allergic reaction.

Adrenaline can be used for the treatment of cardiac arrest. Adrenaline may be used in follow- up treatment in cardiopulmonary resuscitation.

Adrenalin Bradex, 1 mg/ml, Solution for Injection can be given to patients of all ages.

Adrenaline may be injected into a muscle (intramuscularly), into the tissue just beneath the skin (subcutaneously) or into a vein (intravenously).

VI. 2.3 Unknowns relating to treatment benefits

No unknowns relating to treatment benefits.

VI. 2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hypesensitivity	Adrenaline must not be used in case of hypersensitivity to the active substance or to any of the excipients.	Do not use Adrenalin Bradex: if you are allergic to adrenaline or any of the other ingredients of this medicine
Use during labour	Adrenaline must not be used during second stage of labour.	Do not use Adrenalin Bradex when you are in labour.
Use with local anaesthesia of peripheral structures including fingers, toes, ear lobe	Adrenaline must not be used with local anaesthesia of peripheral structures including fingers, toes, ear lobe.	Adrenalin Bradex must not be injected into peripheral parts of the body such as fingers, toes, ear lobes, nose or penis.
Use in the presence of ventricular fibrillation	Adrenaline must not be used in the presence of ventricular fibrillation.	Do not use Adrenalin Bradex if you have ventricular fibrillation.
Use in the presence of cardiac dilatation (a heart problem), coronary insufficiency (a heart problem), organic brain disease or arteriosclerosis, except in emergencies where the potential benefit clearly outweighs the risk.	Adrenaline should not be used in the presence of cardiac dilatation, coronary insufficiency, organic brain disease or arteriosclerosis, except in emergencies where the potential benefit clearly outweighs the risk.	Do not use Adrenalin Bradex if you are suffering from any infection, disease or brain tumour. • if you have atherosclerosis which is a narrowing, and hardening of the body's blood vessels (your doctor will advise you). • if you have ventricular fibrillation or other heart
Use if solution is discoloured.	Adrenaline must not be used if solution is discoloured.	The solution should not be used if it is discoloured.
Repeated injections of adrenaline can cause necrosis as a result of vascular constriction at the injection site. Tissue necrosis may also occur in the extremities (fingers and toes), kidneys and liver.	Repeated local administration of adrenaline may produce necrosis (tissue damage) at the sites of injection.	Adrenaline injection should not be used in areas such as fingers, toes, ears, nose or penis, as the blood supply to these areas might become inadequate.

Concomitant use with oxytocin or other sympathomimetic agents.	Adrenaline should not be administered concomitantly with oxytocin or other sympathomimetic agents because of the possibility of additive effects and increased toxicity.	Talk to your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. A large number of drugs can interact with Adrenalin Bradex which can significantly alter their effects. These drugs include: oxytocin (used to induce labour at term and to control bleeding after delivery). If you are already taking one of these medicines, speak to your doctor before you receive Adrenalin Bradex.

Risk	What is known	Preventability
Use with: • non-cardioselective beta-blocking agents (medicines for controlling blood pressure), due to alpha-mediated vasoconstriction. • Alpha-adrenergic blocking agents (medicines for controlling blood pressure), • tricyclic antidepressants (medicines used for depression), • monoamine oxidase inhibitors (MAOis) (medicines used for depression) • phenothiazines (used to treat mental illness), • cardiac glycosides (medicines used for heart failure), • some antihistamines (eg diphenhydramine) (used for the treatment of allergies) and thyroid hormones (medicines used to treat an underactive thyroid gland), • corticosteroids (medicines used to treat inflammatory conditions in your body such as asthma or arthritis), • potassium-depleting diuretics, • aminophylline and theophylline (medicines to help you breathe), • insulin or oral hypoglycaemic agents (antidiabetic medicines)	**Alpha-adrenergic blocking agents:** Alpha-blockers such as phentolamine antagonise the vasoconstriction and hypertension effects of adrenaline. This effect may be beneficial in adrenaline overdose **Beta-adrenergic blocking agents:** Severe hypertension and reflex bradycardia may occur with non-cardioselective beta-blocking agents such as propranolol, due to alpha-mediated vasoconstriction. Beta-blockers, especially non-cardioselective agents, also antagonise the cardiac and bronchodilator effects of adrenaline. Patients with severe anaphylaxis who are taking non-cardioselective beta-blockers may not respond to adrenaline treatment. **General Anaesthetics:** Administration of adrenaline in patients receiving halogenated hydrocarbon general anaesthetics that increase cardiac irritability and seem to sensitise the myocardium to adrenaline may result in arrhythmias including ventricular premature contractions, tachycardia or fibrillation. **Antihypertensive agents:** Adrenaline specifically reverses the antihypertensive effects of adrenergic neurone blockers such as guanethidine, with the risk of severe hypertension. Adrenaline increases blood pressure and may antagonise	Talk to your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. A large number of drugs can interact with Adrenalin Bradex which can significantly alter their effects. These drugs include: • monoamine oxidase inhibitors (MAOIs) such as moclobemide or tricyclic antidepressants such as imipramine, amitriptyline, medicines used for depression, • cardiac glycosides such as digoxin, used for heart failure, • guanethidine used for the rapid control of blood pressure, • diuretics (“water tablets”) such as hydrochlorothiazide, furosemide, • inhaled general anaesthetics, such as halothane, • medicines to raise or lower blood pressure including beta-blockers, e.g. propranolol, atenolol, bisoprolol, phentolamine, • antidiabetic medicines like insuline and oral hypoglycaemic agents (e.g. glipizide), • aminophylline and theophylline (medicines to help you breathe), • corticosteroids (medicines used to treat inflammatory conditions in your body such as asthma or arthritis), • antihistamines (e.g. diphenydramine) used for the treatment of allergies, • medicines such as chlorpromazine, pericyazine or fluphenazine, used to treat mental illness, • medicines used to treat an

Risk	What is known	Preventability
	the effects of antihypertensive drugs. **Antidepressant agents:** Tricyclic antidepressants such as imipramine inhibit reuptake of directly acting sympathomimetic agents, and may potentiate the effect of adrenaline, increasing the risk of development of hypertension and cardiac arrhythmias. Although monoamine oxidase (MAO) is one of the enzymes responsible for Adrenaline metabolism, MAO inhibitors do not markedly potentiate the effects of adrenaline. **Phenothiazines:** Phenothiazines block alpha-adrenergic receptors. Adrenaline should not be used to counteract circulatory collapse or hypotension caused by phenothiazines since a reversal of the pressor effects of Adrenaline may result in further lowering of blood pressure. **Other drugs:** Adrenaline should not be used in patients receiving high dosage of other drugs (eg cardiac glycosides) that can sensitise the heart to arrhythmias. Some antihistamines (eg diphenhydramine) and thyroid hormones may potentiate the effects of adrenaline, especially on heart rhythm and rate. **Hypokalaemia:** The hypokalaemic effect of adrenaline may be potentiated by other drugs that cause potassium loss, including corticosteroids, potassium-	underactive thyroid gland - any cough or cold remedies (sympathomimetics). If you are already taking one of these medicines, speak to your doctor before you receive Adrenalin Bradex.

Risk	What is known	Preventability
	depleting diuretics, aminophylline and theophylline. **Hyperglycaemia:** Adrenaline-induced hyperglycaemia may lead to loss of blood sugar control in diabetics treated with insulin or oral hypoglycaemic agents.	
Administration of adrenaline in patients receiving halogenated hydrocarbon general anaesthetics.	Administration of adrenaline in patients receiving halogenated hydrocarbon general anaesthetics that increase cardiac irritability and seem to sensitise the myocardium to adrenaline may result in arrhythmias including ventricular premature contractions, tachycardia or fibrillation.	Talk to your doctor, pharmacist or nurse before you are given Adrenalin Bradex if: you are going to have a surgery under general anaesthesia. Speak to your doctor if any of these apply to you before you are given this medicine.
Use in patients with Parkinsonian Syndrome.	In patients with Parkinsonian Syndrome, adrenaline increases rigidity and tremor.	Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects have also been reported (Unknown frequency): increase in rigidity and trembling in patients suffering from a condition called parkinsonian syndrome.
Cardiovascular effects ie, ventricular arrhythmias, disturbances of cardiac rhythm and rate, palpitation, tachycardia, chest pain/ angina, potentially fatal ventricular arrhythmias, fibrillation, decrease in T-wave amplitude	Cardiovascular adverse effects have been identified with the use of adrenaline with unknown frequency ie, ventricular arrhythmias, disturbances of cardiac rhythm and rate, palpitation, tachycardia, chest pain/ angina, potentially fatal ventricular arrhythmias, fibrillation, decrease in T-wave amplitude	It is not possible to prevent this unless the product is stopped.
Cerebrovascular effects; hypertension (with risk of cerebral haemorrhage).	Cerebrovascular effects such as subarachnoid haemorrhage has resulted from hypertension, even following subcutaneous administration of usual doses of adrenaline.	It is not possible to prevent this unless the product is stopped.

Important potential risks

Risk	**What is known**
Use in: • elderly patients, • patients with hyperthyroidism (an overactive thyroid), • diabetes mellitus, • phaeochromocytoma (a tumor on the adrenal gland), • narrow angle glaucoma (high pressure in the eye), • hypokalaemia (low blood levels of potassium), • hypercalcaemia (high blood levels of calcium), • severe renal impairment (kidney disease) and prostatic adenoma (a tumour on prostate gland), • cerebrovascular disease or organic brain damage (problems with the brain e.g. stroke, brain damage or blood vessel disease), • in patients with shock (other than anaphylactic shock), • in organic heart disease or cardiac dilatation (severe angina pectoris, obstructive cardiomyopathy, hypertension) (any heart problem, particularly if it affects the heart rate or angina (chest pain), • in most patients with arrhythmias.	Adrenaline should only be administered with great caution in: • the elderly • patients who suffer from any heart problem, particularly if it affects the heart rate or they suffer from angina (chest pain) • patients having problems with their brain e.g.stroke, brain damage or blood vessel disease • patients with an overactive thyroid, diabetes or glaucoma (high pressure in the eye) • patients with phaeochromocytoma (a tumor on the adrenal gland) • patients who have low blood levels of potassium or high blood levels of calcium • patients who have a tumor on the prostate gland or kidney disease • patients in shock or have lost a lot of blood • patients who are going to have a surgery under general anaesthesia • patients who are suffering from high blood pressure.
Anginal pain maybe induced when coronary insufficiency is present.	Pain in the chest maybe induced when coronary insufficiency is present.
Prolonged administration may induce metabolic acidosis (an imbalance of certain constituents in the blood), renal necrosis (kidney damage) and adrenaline-fastness or tachyphylaxis.	Prolonged administration of adrenaline may induce metabolic acidosis (an imbalance of certain constituents in the blood), renal necrosis (kidney damage) and adrenaline-fastness or tachyphylaxis.
Use during the second stage of labour.	Adrenaline 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. Parenteral Adrenaline should not be used during the second stage of labour.

Missing information

There is no missing information.

VI. 2.5 Summary of risk minimisation measures by safety concern

Further details about how to use Adrenalin Bradex, 1 mg/ml, Solution for injection, the risks and recommendations for minimising them can be found in the leaflet supplied with the medicine. The measures in this document are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI. 2.6 Planned post authorization development plan

There are no planned efficacy studies or further investigation of safety concerns.

VI. 2.6 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
First	At time of authorisation	Identified Risks Potential Risks Missing information identified and summarised	New document

Summary EU-Risk Management Plan