Prescribing Information (Summary of Product Characteristics)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
1.1 PRODUCT NAME

ADRENALINE INJECTION BP 1 MG/ML, 1 ML

1.1 STRENGTH 1.0 mg/ml

1.2 PHARMACEUTICAL FORM
Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
2.1 QUALITATIVE DECLARATION

Adrenaline Acid Tartrate BP
Equivalent to Adrenaline

2.2 QUANTITATIVE DECLARATION

Each ml contains:
Adrenaline Acid Tartrate BP
Equivalent to Adrenaline 1.0 mg
Water for injections BP q.s.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Dosage form: Solution for Injection

Description: A clear and colourless solution, free from visible particles and fibers.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Indication:
Adrenaline Injection BP 1 in 1000 may be used in the treatment of acute allergy and anaphylactic shock.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The intramuscular route is the preferred choice for most individuals who have to be given adrenaline for the management of an anaphylactic reaction. The generally accepted dosage of adrenaline in this indication is 0.01mg/kg body weight. An additional dosage table according to age is presented below.

4.3 CONTRAINDICATIONS

Hypersensitivity to adrenaline, sodium metabisulfite or any of the other ingredients.
Adrenaline 1 in 1000 should not be used in fingers, toes, ears, nose or genitalia owing to the risk of ischaemic tissue necrosis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Adrenaline should be used with caution in patients with:
• hyperthyroidism, psychoneurosis, phaeochromocytoma, narrow angle glaucoma, diabetes mellitus, hypokalaemia or hypercalcaemia.
• severe renal impairment, prostatic hypertrophy or urination difficulty
• cerebrovascular disease, organic brain damage or arteriosclerosis
• autonomic dysreflexia (hyperreflexia), particularly in spinal cord injury (e.g., tetraplegics)
• shock (other than anaphylactic shock)
•organic heart disease or cardiac dilatation (severe angina pectoris, obstructive cardiomyopathy, hypertension) as well as most patients with arrhythmias. Anginal pain may be induced when coronary insufficiency is present.
Adrenaline should be used with caution in older patients
Adrenaline should be used with extreme caution in patients with long-standing bronchial asthma and emphysema who have developed degenerative heart disease.
Adrenaline should be used cautiously, if at all, during general anaesthesia with halogenated hydrocarbon anaesthetics.
Adrenaline should not be used during the second stage of labour.
Accidental intravascular injection may result in cerebral haemorrhage due to the sudden rise in blood pressure.
The IM route is generally preferred in the initial treatment of anaphylaxis, the IV route is generally more appropriate in the Intensive Care Unit (ICU) or Emergency Department (ED) setting.
Adrenaline (epinephrine) injection 1:1000 (1mg/ml) is not suitable for IV use. If the epinephrine 1:10000 (0.1mg/ml) injection is not available, epinephrine injection 1:1000 must be diluted to 1:10000 before IV use. The IV route for injection of epinephrine must be used
with extreme caution and is best reserved for specialists familiar with IV use of epinephrine (adrenaline).
Monitor the patient as soon as possible (pulse, blood pressure, ECG, pulse oximetry) in order to assess the response to adrenaline.
The best site for IM injection is the anterolateral aspect of the middle third of the thigh. The needle used for injection needs to be sufficiently long to ensure that the adrenaline is injected into muscle.
Intramuscular injections of Adrenaline into the buttocks should be avoided because of the risk of tissue necrosis.
Prolonged use of Adrenaline can result in severe metabolic acidosis (because of elevated blood concentrations of lactic acid), renal necrosis and tachyphylaxis.
Adrenaline Injection contains sodium metabisulfite, which can cause allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic episodes, in certain susceptible individuals.

The presence of sodium metabisulfite in parenteral Adrenaline 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.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION FORMS OF INTERACTION

Sympathomimetic agents:
Adrenaline should not be administered concomitantly with other
sympathomimetic agents because of the possibility of additive effects and increased toxicity.
Alpha-adrenergic agents:

The vasoconstrictor and pressor effects of adrenaline, mediated by its alphaadrenergic action, may be enhanced by concomitant administration of drugs with similar effects, such as ergot alkaloids or oxytocin.

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. Adrenaline specifically reverses the antihypertensive effects of adrenergic neurone blockers such as guanethidine with the risk of severe hypertension.

Beta-adrenergic blocking agents:
Severe hypertension and reflex bradycardia may occur with noncardioselective beta-blocking agents such as propranolol, due to alphamediated 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 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.

Concurrent use or use within 2 weeks of a monoamine oxidase inhibitor increases the risk of adverse events.

Phenothiazines:
Phenothiazines block alpha-adrenergic receptors (see above). Adrenaline should not be used to counteract circulatory collapse or hypotension caused by phenothiazines; 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 (e.g. cardiac glycosides) that can sensitise the heart to arrhythmias. Some antihistamines (e.g. diphenhydramine) and thyroid hormones may potentiate the effects of Adrenaline, especially on heart rhythm and rate. Adrenaline increases the risk of cardiac adverse effects of levodopa. Use of Entacapone may potentiate the chronotropic and arrhythmogenic effects of adrenaline.

Hypokalaemia:
The hypokalaemic effect of adrenaline may be potentiated by other drugs that cause potassium loss, including corticosteroids, potassium-depleting diuretics, aminophylline and theophylline.

Hyperglycaemia:
Adrenaline-induced hyperglycaemia may lead to loss of blood-sugar control in diabetic patients treated with insulin or oral hypoglycaemic agents.

4.6 PREGNANCY AND LACTATION

Pregnancy
Adrenaline crosses the placenta. There is some evidence of a slightly increased evidence of congenital abnormalities. Injection of adrenaline may cause anoxia to the foetus, foetal tachycardia, cardiac irregularities, extrasystoles and louder heart sounds.
Adrenaline 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. For this reason parenteral Adrenaline should not be used during the second stage of labour. Adrenaline should only be used during pregnancy if the potential benefits justify the possible risks to the foetus.

Lactation
Adrenaline is distributed into breast milk. Breast-feeding should be avoided in mothers receiving Adrenaline injection. There are limited data from the use of hyoscine butylbromide in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. As a precautionary measure Hyoscine Butylbromide is not recommended during pregnancy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients' ability to drive and use machines may be affected by the anaphylactic reaction, as well as by possible adverse reactions to adrenaline.

4.8 UNDESIRABLE EFFECTS

The adverse events of adrenaline mainly relate to the stimulation of both alpha- and beta-adrenergic receptors. The occurrence of undesirable effects depends on the sensitivity of the individual patient and the dose involved.

Immune system disorders:
Anaphylaxis, possibly with severe bronchospasm.

Metabolism and nutrition disorders:
Hypokalaemia, metabolic acidosis.
Inhibition of insulin secretion and hyperglycaemia even with low doses, gluconeogenesis, glycolysis, lipolysis and ketogenesis.

Psychiatric disorders:
Psychotic states, anxiety, fear, confusion, irritability, insomnia, restlessness

Nervous system disorders:
Headache, dizziness, tremors
In patients with Parkinsonian Syndrome, Adrenaline increases rigidity and tremor. Subarachnoid haemorrhage and hemiplegia have resulted from hypertension, even following subcutaneous administration of usual doses of Adrenaline.

Cardiac disorders:
Disturbances of cardiac rhythm and rate may result in palpitation and tachycardia. Adrenaline can cause potentially fatal ventricular arrhythmias including fibrillation, especially in patients with organic heart disease or those receiving other drugs that sensitise the heart to arrhythmias. Myocardial ischaemia and myocardial infarction have been reported. Adrenaline causes E.C.G. changes including a decrease in T-Wave amplitude in all leads in normal subjects.
In rare cases stress cardiomyopathy has been seen in patients treated with adrenaline.

Vascular disorders:
Hypertension (with risk of cerebral haemorrhage). Coldness of extremities may occur even with small doses of Adrenaline. Bowel necrosis

Respiratory disorders:
Dyspnoea. Pulmonary oedema may occur after excessive doses or in extreme sensitivity.
Gastrointestinal disorders: Dry mouth, reduced appetite, nausea, vomiting, hypersalivation.

Renal and urinary disorders:
Difficulty in micturition, urinary retention.

General disorders and administrative site conditions:
Sweating, weakness, pallor. 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, kidneys and liver.

4.9 OVERDOSE

Symptoms
After overdosage or inadvertent intravenous administration of usual intramuscular subcutaneous doses of Adrenaline, systolic and diastolic blood pressure rise sharply; venous pressure also rises.
Cerebrovascular or other haemorrhages and hemiplegia may result, especially in elderly patients. Pulmonary oedema may occur. Adrenaline overdosage causes transient bradycardia followed by tachycardia and may cause other potentially fatal cardiac arrhythmias. Kidney failure, metabolic acidosis and cold white skin may also occur.

Treatment
Because Adrenaline is rapidly inactivated in the body, treatment of acute toxicity is mainly supportive. The pressor effects of Adrenaline may be counteracted by an immediate intravenous injection of a quick-acting alpha adrenoreceptor blocking agent, such as 5-10 mg of phentolamine
mesylate, followed by a beta-adrenoreceptor blocking agent, such as 2.5 - 5 mg of propranolol. Arrhythmias, if they occur, may be counteracted by propranolol injection.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS PROPERTIES
Pharmacotherapeutic Group: adrenergic and dopaminergic agents, adrenaline.

ATC code: C01CA24

Adrenaline is a naturally occurring catecholamine secreted by the adrenal medulla in response to exertion or stress. It is a sympathomimetic amine which is a potent stimulant of both alpha- and beta-adrenergic receptors and its effects on target organs are therefore complex. It is used to provide rapid relief of hypersensitivity reactions to allergies or to idiopathic or exercise-induced anaphylaxis.
Adrenaline has a strong vasoconstrictor action through alphaadrenergic stimulation. This activity counteracts the vasodilatation and increased vascular permeability leading to loss of intravascular fluid and subsequent hypotension, which are the major pharmacological features in anaphylactic shock. Adrenaline stimulates bronchial beta-adrenergic receptors and has a powerful bronchodilator action. Adrenaline also alleviates pruritus, urticaria and angioedema associated with anaphylaxis.

5.2 PHARMACOKINETIC PROPERTIES

Adrenaline has a rapid onset of action after intramuscular administration and in the shocked patient its absorption from the intramuscular site is faster and more reliable than from the subcutaneous site. Adrenaline is rapidly inactivated in the body, mostly in the liver by the enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). Much of a dose of adrenaline is excreted as metabolites in urine. The plasma half-life is about 2-3 minutes. However, when given by subcutaneous or intramuscular injection, local vasoconstriction may delay absorption so that the effects may last longer than the half-life suggests.

6. PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS(S)

Sodium Chloride BP
Sodium Metabisulphate BP
Di-Sodium EDTA BP
Water for injections BP

6.2 INCOMPATIBILITIES

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

6.3 SHELF-LIFE
24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C.

KEEP OUT OF REACH AND SIGHT OF CHILDREN

6.5 NATURE AND CONTENTS OF CONTAINER

10 x 1 ml amber glass Ampoules packed in a carton along with plastic tray & insert.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER
Discard any unused portion immediately after use.

7. MARKETING AUTHORISATION HOLDER

Swiss Parenterals Ltd
808, 809 & 810, Kerala Industrial Estate, GIDC,
Nr. Bavla, City: Ahmedabad
Dist. Ahmedabad-382 220.
India.

8. MARKETING AUTHORISATION NUMBER
TAN 20 HM 0539

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
18/11/2020

10. DATE OF REVISION / APPROVAL OF THE TEXT