1. NAME OF THE DRUG
Isoprenaline hydrochloride S.A.L.F. 0.2 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ampoule contains:
Active ingredient: Isoprenaline hydrochloride 0.2 mg.
For a full list of the excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
The solution is clear and colorless.

4. CLINICAL INFORMATION
4.1 Therapeutic indications
Treatment for total atrioventricular block (including the Stokes-Adams syndrome) and cardiac arrest.
Treatment for bronchospasm during anesthesia.
In addition to a treatment for cardiogenic shock.

4.2 Posology and method of administration
Treatment for total atrioventricular block (including the Stokes-Adams syndrome) and cardiac arrest.
Intramuscular administration: 0.2 mg followed by 0.02 to 1.0 mg depending on the patient's response.
Intravenous administration: 2-10 micrograms/min, which could be adjusted according to the patient's response.
Subcutaneous administration: 0.2 mg followed by 0.15-0.2 mg depending on the patient's response.

Treatment for bronchospasm during anesthesia.
Intravenous administration: initial dose 0.01-0.02 mg, repeated if necessary.

In addition to a treatment for cardiogenic shock.
Intravenous administration: 0.5-5 micrograms/min, depending on the patient's response. Higher doses (up to 20 micrograms/minute) can be sometimes used in severe states of shock according to the clinical conditions and the patient's response.
The use of Isoprenaline is not recommended in children due to a lack of data on safety and efficacy.

Instructions for use

For intravenous injection
Dilute 1 ml of Isoprenaline hydrochloride 0.2 mg/ml solution for injection with 10 ml of 0.9% sodium chloride or 5% glucose to obtain a solution with a concentration of 0.02 mg/ml.

For intravenous infusion
Dilute 10 ml of Isoprenaline hydrochloride 0.2 mg/ml solution for injection with 500 ml of 0.9% sodium chloride or 5% glucose to obtain a solution with a concentration of 0.004 mg/ml.
Use a microdrip or a continuous infusion pump to prevent a sudden inflow of an excessive amount of drug.

4.3 Contraindications
Hypersensitivity to the active ingredient(s) or to any of the excipients.
Isoprenaline is contraindicated in the following conditions:
- Angina pectoris;
- Heart block or tachycardia induced by digitalis drugs;
- Tachyarrhythmias.

Children under the age of 12 years.
Generally contraindicated in pregnancy and lactation (see 4.6).

4.4 Special warnings and precautions for use
Use extreme caution when administering the drug in the following situations:
- Seizure disorders;
- Coronary insufficiency;
- Diabetes mellitus;
- Hyperresponsiveness to sympathomimetic amines;
- Hypertension;

- Hyperthyroidism.

For anyone who plays sports: the use of this drug without therapeutic need is doping, it may cause doping effects and positive doping tests also with therapeutic doses.

Important information about some of the ingredients:
The solution of Isoprenaline hydrochloride S.A.L.F. contains sodium metabisulfite, a sulfite that may cause allergic reactions, including anaphylactic or life-threatening symptoms or severe asthmatic episodes in susceptible patients.
This medicinal product contains less than 1 mmol (23 mg) of sodium, i.e. it is essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction
Isoprenaline should not be given concurrently with:
- cardiac glycosides and general anesthetics (halothane, cyclopropane): concomitant use may cause arrhythmias;
- ergot alkaloids: concomitant use may result in further peripheral vasoconstriction;
- phenelzine, selegiline, tranylcypromine: concomitant use with any of these drugs may increase the hypertensive effect due to a decreased sympathomimetic metabolism. Therefore, it is necessary to monitor patients in the presence of clinical effects indicating a rise in blood pressure (headache, arrhythmias, fever, vomiting). If a hypertensive crisis occurs, immediately stop the administration of the drug and start a therapy to lower blood pressure.
- entacapone: concomitant use may result in an increased risk of tachycardia, hypertension and arrhythmias due to the inhibition of the COMT metabolism.
- nebivolol: concomitant use with this drug can cause a change in the beta-blocker effect and cause severe hypotension due to a mechanism of pharmacological antagonism derived from the vasodilatory effects of Isoprenaline. Therefore, it is necessary to closely monitor patients being treated with these two drugs.
- theophylline: concomitant use with this drug may cause a decrease of the theophylline concentration due to an increase in metabolism. Therefore, adjustments to the dose of theophylline could be necessary.
- tolcapone: concomitant use with this drug can cause the inhibition of the Isoprenaline metabolism due to COMT inhibition by tolcapone. Therefore, a reduction in the dose of Isoprenaline should be considered in patients taking tolcapone.

4.6 Pregnancy and lactation
Pregnancy
Animal studies are insufficient with respect to effects on pregnancy and fetal development (see section 5.3). The potential risk for humans is not known.
Isoprenaline should not be used during pregnancy, unless clearly necessary. Since Isoprenaline is used as a life-saving in cardiac emergencies, the risk/benefit ratio is not in question. Isoprenaline easily crosses the placenta and may inhibit uterine contractions and delay preterm birth.

Lactation
It is not known whether Isoprenaline is excreted in breast milk and there are no known potential adverse effects that would occur in newborns after exposure to this drug. It is not known if Isoprenaline affects the amount or composition of breast milk. Until further data become available, caution must be used when administering Isoprenaline during lactation.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Side effects
Here below are the possible side effects of Isoprenaline organized according to MedDRA system organ classification. There are insufficient data to determine the frequency of the each single effect listed.

Cardiac disorders
Palpitations, tachycardia, changes in blood pressure, ventricular arrhythmias and Adam-Strokes syndrome in patients with transient atrioventricular block, cardiac arrest.

Gastrointestinal disorders
Nausea, gastrointestinal distress.

Blood and lymphatic system disorders
Thrombocytopenia, eosinopenia (studies in healthy volunteers).

Nervous system disorders
Tremors, dizziness, nervousness, drowsiness, headache and insomnia.

Eye disorders
Blurred vision.

Renal and urinary disorders
Urinary hesitancy.

Respiratory, thoracic and mediastinal disorders
Cough, sore throat, bronchitis, increased sputum, pulmonary edema.

Endocrine disorders
Swelling of the parotid gland after prolonged use, discoloration of saliva.

Skin and subcutaneous tissue disorders
Sweating and skin redness.

4.9 Overdose
An overdose of Isoprenaline can cause tremors, palpitations, angina, arrhythmias, tachycardia, an increase or a decrease in blood pressure, seizures, nervousness, headache, dry mouth, nausea, dizziness, fatigue, malaise and insomnia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: adrenergic and dopaminergic agents.
ATC code: C01CA02
Isoprenaline causes bronchodilation with a bronchial muscle relaxation through a stimulation of the beta-2 receptors, it increases the heart rate and the myocardial contractility by stimulating beta-1 receptors, thereby also increasing the cardiac output.

5.2 Pharmacokinetic properties
Absorption
It is rapidly absorbed through intramuscular or subcutaneous injection.

Metabolism
From 25% to 35% of the Isoprenaine administered is metabolized in the liver and other tissues by COMT to 3-O-methyl-isoprenaline, an inactive metabolite which is excreted unchanged in the urine or as sulfate conjugate.
In children, 77% -87% of the dose of Isoprenaline is converted after an hour to its metabolite conjugate, which is then eliminated through urinary excretion after 2 hours.

Excretion
After an intravenous administration, approximately 50% of the dose is excreted unchanged in the urine. In children, a high proportion of unchanged drug is present in the urine after 5 minutes. More than 80% of the metabolite conjugate is eliminated after 2 hours, especially as 3-O - methyl-isoprenaline.

5.3 Preclinical safety data
Preclinical data have little clinical relevance in light of the extensive experience gained with the use of the drug in humans.

6. PHARMACEUTICALINFORMATION

6.1 List of the excipients
Lactic acid 90%
Sodium lactate 60%
Sodium metabisulfite
Water for injections.

6.2 Incompatibilities
Isoprenaline should not be mixed together with medical solutions with alkaline pH (e.g. sodium bicarbonate, aminophylline, basic buffered antibiotics), because, under conditions of pH greater than 6, the oxidation rate increases considerably.
There are conflicting data regarding the incompatibility of Isoprenaline administered concomitantly with doxycycline and secobarbital. In any case, the solution of Isoprenaline should be administered immediately after its preparation.

6.3 Shelf life
2 years in unopened package.

6.4 Special precautions for storage
Store in the original package in order to repair it from light.
Store at room temperature not exceeding 15° C.
If exposed to air, to light or to an increase in temperature, the solution can develop a color ranging from pink to brownish pink. The solution should not be used if it is colored or a precipitate is present.

6.5 Nature and contents of container
Glass ampoule of 1 ml.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
S.A.L.F. S.p.A. Laboratorio Farmacologico - Via Marconi, 2 - Cenate Sotto (BG) - Tel 035-940097

8. MARKETING AUTHORISATION NUMBER
5 ampoules of 1 ml - A.I.C. 030674016

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
May 5th, 2008

10. DATE OF REVISION OF THE TEXT
August 2012