Summary of Product Characteristics

1. **NAME OF MEDICINAL PRODUCT**
   Protamine Sulphate 1%
   Solution for intravenous injections
   10 mg/ml

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION OF ACTIVE SUBSTANCES**
   1 ml of solution contains:
   - Protamine Sulphate 10 mg
   5 ml of solution contain:
   - Protamine Sulphate 50 mg
   Detailed list of excipients, see item 6.1.

3. **PHARMACEUTICAL FORM**
   Solution for injections.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications
   Protamine Sulphate 1 % is used to counteract the anticoagulant effect of heparin.

4.2. Posology and method of administration

   **Posology**
   1 mg of protamine sulphate counteracts the anticoagulant effect of approximately:
   - 90 international units of heparin sodium, heparin obtained from lung tissue of cows,
   - 100 international units of heparin calcium obtained from intestine mucosa of pigs.
   Concentration of heparin in the serum drops quickly because of its half-life period is short.
   A dose of Protamine Sulphate 1% depends on the lapse of time from intravenous injection
   of heparin and its quantity.
   Approx. 1 mg of protamine is required to neutralize 100 IU of heparin.
   It is recommended to adjust (calculate) the dose of protamine sulphate on the basis of its
   titration with heparin in vitro with simultaneous measurement of activated coagulation time
   (ACT).

   **Method of administration:**
   Only for intravenous injections.
   Protamine sulphate 1% administered by another way does not neutralise heparin.
   Regardless of the method of administration of heparin (intravenously, intradermally,
   subcutaneously) there should be injected intravenously the content of one ampoule (5 ml)
   of Protamine Sulphate 1 %.
   If necessary, the injection may be repeated once or more times in 10-15 minutes intervals.
After subcutaneous or intramuscular administration of heparin, when its action is prolonged, it is necessary to repeat injection of protamine sulphate after 3 hours. Supplementary doses should be calculated and administered depending on the patient’s blood coagulation tests results (APTT, ACT) which are recommended to be performed within 5 to 15 minutes after administration of the product Protamine Sulphate 1%.

4.3. Contraindications
Protamine Sulphate 1% should not be applied in patients with:

- the symptoms of intolerance of the preparation after its prior injection,
- the presence of anti protamine antibodies in blood serum,
- fish allergies.

One should not administer Protamine Sulphate 1% to patients with diabetes which are administered or have been administered insulin preparations containing protamine. In such patients exists the risk of acute undesirable effects including anaphylactic ones. In case it is necessary to perform heart surgery in patients in which it is presumed protamine sulphate intolerance, one should consider application of another method of heparin neutralisation or administration of another substance neutralising heparin.

4.4. Special warnings and special precautions for use
One should not exceed the velocity of administration of the preparation:

- 10 mg/ml not quicker than 3 minutes,
- 50 mg/ml not quicker than 10 minutes.

Intervals between following doses in the quantity of 50 mg of protamine sulphate per 1 ml should be 10 ÷ 15 minutes.

Too quick administration of the preparation may cause escalation or occurrence of acute undesired effects.

The dose of 50 mg of protamine sulphate should not be exceeded within the first 10 minutes, in order to decrease the risk of undesired effects.

The preparation should be administered slowly: too quick injection escalates undesired effects. It is recommended that the average dose of 50 mg is administered within 10 minutes (not quicker).

4.5. Interactions with other medicaments and other forms of interactions
Protamine sulphate 1% shows incompatibility with some antibiotics, mainly penicillin derivatives and cephalosporins with amidotrizoic and ioxalgc acids and their derivatives applied in diagnostics.

4.6. Pregnancy and lactation
No sufficient data concerning application of Protamine Sulphate 1% in pregnant and lactating women.
Precautions should be taken when prescribing the medicament to pregnant and lactating women.

**4.7. Effects on ability to drive motor vehicles and operate machines**
Not applicable as the patients being administered Protamine Sulphate 1% are hospitalized post cardiovascular surgical treatment.

**4.8. Undesirable effects**
After administration of Protamine Sulphate 1% there may occur short-lasting and average intensity undesirable effects, usually in the cardiovascular system.

The most frequent are:
- hypotension – fall in blood pressure; generally slight and passing,
- hypotension with bradycardia (heart slowness) - slight and passing,
- temporary slowing of heart work,
- reddening, feeling of heat,
- short-lasting hemodynamics (circulation) disorders.

The mechanism of these reactions has not been specified.

The heparin/protamine complex may split, in the result of which there may occur hyperheparinaemia or haemorrhage. Release of heparin from the complex causes activation of antitrombin acting as an anticoagulant. Such reaction takes place within 30 minutes to 18 hours after heart surgeries. In order to prevent the release of heparin one should administer supplementary dose of protamine sulphate whose quantity is to be determined on the basis of the laboratory test of patient’s blood coagulation.

It is estimated that breaking the complex heparin/protamine exists in approx. 50% cases after heart surgeries.

Despite many trials, the mechanism of this phenomenon has not been discovered yet.

It was observed that breaking of the complex heparin/protamine occurs more rarely if there is administered a slight excess of Protamine Sulphate 1% (as compared with the titration), immediately after completion of extracorporal circulation.

Very rarely may occur passing:
- leucopenia and thrombocytopenia,
- weariness,
- backache,
- nausea,
- vomits,
- dyspnoea,
- panting,
- contraction of bronchi,
- hives,
- reddening of the skin.
- There may also occur single cases of oedema, hypertension with contraction of pulmonary vessels.
- There is also the risk of anaphylactic reactions in patients with allergy to protamine, fish allergies in which was discovered anti protamine antibodies, in patients with diabetes who were administered protamine insulin.

Such reactions may appear after injection of 15 to 35 mg of Protamine Sulphate 1%. In these patients, before any surgical treatment, one should perform proper skin tests for hypersensitivity (allergy) to protamine. In case it is stated the allergy to protamine, one should consider application of another method of heparin neutralisation or administer another substance neutralising the activity of heparin.

In case of allergic reactions good results are obtained after application of adrenalin and corticosteroids.

It is estimated that the number of acute anaphylactic reactions in patients with diabetes treated with protamine insulin is 3.0 % and approx. 0.2 % in patients, who were not administered protamine.

4.9. **Overdose**

It is considered proper to apply slight excess of Protamine Sulphate 1%. Too big excess may escalate the anticoagulative result.

No overdose case was reported.

5. **PHARMACOLOGICAL PROPERTIES**

Protamine sulphate 1% is a mixture of simple, basic polypeptides. These proteins are built of aminoacids, mainly arginine, approx. 65%, which is responsible for high alkalinity of protamine sulphate, alanine and serine. Most protamines contain proline, valine, many of them also contain glycine and isoleucine. They do not contain tyrosine and tryptophan.

Protamines sulphate 1% as an aminoacidic polycationic preparation easily binds with heparin which is a polyanionic mucopolysaccharide acting as an anticoagulant through activation of antithrombin III.

Heparin action is used in surgery during surgical operations on an open heart, main vascular system or lungs with the application of extracorporal circulation.

In order to neutralise the anticoagulant activity of heparin, directly before disconnection of the heart-lung machine there is applied protamine sulphate. It also demonstrates anticoagulant action through interaction with thrombocytes, fibrinogen other blood proteins, however much weaker than action of heparin.

This action should be considered when determining the dose of Protamine Sulphate 1%, which should be minimal, however completely neutralising heparin. Generally it is assumed that 1 mg of protamine sulphate neutralises 100 units of heparin.
The heparin half-life period depends on the dose; e.g. 100 units/kg of body mass loses its activity after 1 hour after intravascular injection. Protamine does not neutralise completely the activity of low molecular weight heparins.

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antidota, ATC code: **V03A B14**

Protamine sulphate 1% demonstrates activity neutralising anticoagulant properties of heparin, creating the complex heparin/protamine.

Activity of protamine (towards heparin) takes place within five minutes after intravenous injection of the preparation.

The preparation is injected at the end of the work of the pump of the apparatus for extracorporeal circulation. Neutralisation of heparin should be performed under strict supervision of the doctor and laboratory, especially as regards the activated partial thromboplastin time (APTT) or activated clotting time (ACT), in order to restore normal, physiological ability of coagulation i.e. clotting of the blood.
5.2. Pharmacokinetic properties

General characteristic of studies performed
Protamine sulphate 1% has been used for over 30 years. The in vitro and in vivo tests of neutralisation of heparin by protamine were widely published in 1970’s to 1990’s. Despite differences in opinions and results, there have been defined an average neutralising dose of protamine sulphate amounting to 1 mg per each 100 units of heparin. It has also been tested that the dose of Protamine Sulphate 1% should be determined depending on the lapse of time from the last administering of heparin, which has a very short half-life period: from 1 to 3 hours.

On the basis of many years clinical observations there have been determined the type and severity of undesired effects and the method of handling patients in such cases.

While the mechanism of occurrence of undesired effects, metabolism and protamine elimination have not been know yet.

Absorption
Protamine Sulphate gets into the circulation immediately after intravenous injection.

Distribution
With the circulatory system. The preparation acts in the vascular system binding heparin.

Metabolism
The metabolism of the complex protamine/heparin and protamine has not been discovered. It is presumed that the complex and protamine are partially disintegrated with the surplus protamine or are decomposed in the fibrinolytic system (by fibrinolysin).

Elimination/excretion
The mechanism has not been discovered yet.

5.3. Preclinical safety data

The preparation has been applied for 40 years.
Its ability to neutralise heparin used in cardiovascular surgical treatment in extracorporeal circulation is well known. There are also known undesired effects, mainly short-lasting hemodynamic reactions. The tests performed on animals generally aim at discovery of the mechanisms of undesired effects or replacement of heparin and protamine with other compounds with the same properties.

Clinical trials on humans are carried out in order to specify the minimal, yet efficient dose, preventing release of heparin from the complex heparin/protamine, reduction of the reaction of protamine intolerance and replacement of both compounds with other ones.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients
Water for injections

6.2. Pharmaceutical Incompatibilities
Protamine Sulphate 1% should not be administered together with other drugs. Protamine shows incompatibility with some antibiotics, mainly penicillin derivatives and cephalosporins with amidotrizoic and ioxalgie acids and their derivatives applied in diagnostics.

6.3. **Shelf Life**

2 years

Do not use after the validity date.

6.4. **Special precautions for storage**

Store in temperature below 25°C. Do not keep in refrigerator. Do not freeze.

6.5. **Nature and contents of the container**

Glass ampoule 5 ml in cardboard box.

6.6. **Instruction concerning preparation of the medicinal product for application and disposing of its residues**

Intravenous injections

All residues of unused product or its wastes should be disposed according to the applicable local regulations.

7. **MARKETING AUTHORISATION HOLDER**

Wytwórnia Surowic i Szczepionek BIOMED Sp. z o.o.,

00 - 725 Warszawa (Warsaw), ul. Chełmska 30/34.

Tel. 022 841 40 71

8. **MARKETING AUTHORISATION NUMBERS**

639/S.

R/2240

**DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

1 August 1968

17 June 1999

23 September 2004

24 May 2005

**DATE OF APPROVAL OR PARTIAL REVISION OF THE TEXT OF SUMMARY OF PRODUCT CHARACTERISTICS**