Summary of Product Characteristics

Sodium Phosphate (\(^{32}\text{P}\)) 18.5-185 MBq/ml Injection

1. NAME OF THE MEDICINAL PRODUCT

Sodium Phosphate (\(^{32}\text{P}\)) 18.5-185 MBq/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium Phosphate (\(^{32}\text{P}\)) Injection is a sterile, isotonic sodium phosphate solution for intravenous use. The specific activity is greater or equal to 11.1 MBq/ mg of orthophosphate ion.

Active ingredient: Sodium phosphate (\(^{32}\text{P}\))

Composition per ml:
- Orthophosphate (\(^{32}\text{P}\)) stock solution 18.5-185 MBq
- Disodium hydrogen phosphate, dihydrate < 0.1 mg
- Sodium dihydrogen phosphate, monohydrate < 0.4 mg
- Sodium chloride solution for injection 0.9% ad 1.0 ml

The physical characteristics of P-32: The half-life of P-32 is 14.29 days and it decays solely with the emission of beta particles, with a mean energy of 0.695 MeV \((E_{\text{max}} = 1.71 \text{ MeV})\), to stable sulfur.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

a) Polycythemia Rubra Vera

Palliative treatment of primary proliferative polycythemia and / or essential thrombocythemia.

b) Palliative treatment of bone pain secondary to metastatic deposits.

Radioactive phosphorus is indicated for the treatment of terminally ill patients who have not responded to conventional therapies (hormones, wide or narrow beam
radiotherapy, cytotoxins etc.). These patients present with widespread painful bone metastases from assorted primaries and require or are likely to require increasing quantities of strong analgesics.

4.2 Posology and method of administration

Sodium phosphate ($^{32}$P) solution for injection must be administered carefully as an intravenous injection and it must be followed by a saline flush to prevent venous thrombophlebitis. An inadvertently administered subcutaneous injection may lead to radio-necrosis of the surrounding tissues.

The activity to be administered is determined by clinical judgment which should be based on the clinical indication, the size and general health of the patient and the stage and severity of the primary illness.

a) Polycythemia Rubra Vera

The usual initial intravenous dose is 100 MBq/ body surface area (m$^2$). The recommended maximum activity is 185 MBq. However, initial activities of 74 - 260 MBq have been used. A repeat dose of $^{32}$P may be indicated if the hematological response achieved is inadequate. The repeat dose should not be considered until the total clinical efficacy of the initial treatment has been evaluated; usually after 3 to 4 months. It is recommended that the activity should not exceed 125% of the initial activity, and that the annual cumulative activity of $^{32}$P does not exceed 740 MBq. Higher doses may be justifiable occasionally.

Venesection might also be indicated for patients in hypercoagulative states, particularly where significant clinical symptoms are present or the patient is at risk of serious thrombotic episodes.

b) Metastatic bone illnesses

Bone pain may be controlled by doses of 370-555 MBq, administered at 3-4 month intervals, when other therapy such as hormone treatment, chemotherapy or radiotherapy have failed. It may take a few weeks before the reduction in bone pain becomes apparent and it may be associated with increased treatment compliance and reduced used of analgesics.

4.3 Contraindications

Children, pregnancy and breastfeeding are absolute contraindications.

4.4 Special warnings and special precautions for use

The administration of $^{32}$P is not usually recommended to patients under the age of 50. It should be taken into consideration that polycythemia rubra vera can also be alleviated by repeated venesections, thioureas and regular courses of oral
chlorambucil. When treating painful bone metastases in prostatic carcinoma more suitable radiopharmaceutical agents might be available.

Since the effective half-life of $^{32}$P is relatively long, it should not be administered to patients whose expected survival time is short.

Receiving the delivery, handling and administration of the product are limited to authorized personnel. Rules and regulations issued by the authorities must be adhered to when receiving, storing, handling, transferring or disposing of the product.

Radiopharmaceuticals should be prepared by the operator in a manner which satisfies both radiation safety and pharmaceutical quality requirements.

Since treatment with radioactive phosphorus may cause delayed bone marrow depression, cytotoxic agents should not be administered until four months have elapsed since $^{32}$P treatment.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism and retention of labeled $^{32}$P may be affected by the use of estrogen and androgen preparations.

4.6 Pregnancy and lactation

When radioactive medicinal products are to be administered to women of childbearing potential, the possibility of pregnancy must first be ruled out. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionizing radiation should also be considered. The patient should avoid pregnancy for at least three months following the cessation of $^{32}$P treatment due to myeloproliferative disturbances. Patients who have received the maximum of 300 MBq of $^{32}$P should avoid pregnancy for three months following the treatment and those who have received higher doses of activity should increase the "withdrawal period".

Pregnancy: There are no human or animal study data but the recommended radioactive doses of $^{32}$P are considered to be both mutagenic and teratogenic. The administration of $^{32}$P is therefore contraindicated during pregnancy.

Breastfeeding: This radioactive substance should not be administered to patients who wish to continue breastfeeding. Before administering a radioactive medicinal product to a mother who is breastfeeding, consideration should be given to whether the investigation could be delayed until the mother has ceased breastfeeding and to whether the most appropriate choice of radiopharmaceutical has been made. If the
administration of the medicine is considered imperative, breastfeeding must be stopped and replaced with e.g. formula feeding. Milk may be expressed for future use before the administration of the medicine.

4.7 Effects on ability to drive and use machines

The product has no effect on ability to drive or use machines.

4.8 Undesirable effects

For each patient, exposure to ionizing radiation must be justifiable on the basis of likely benefit. The dose administered must be such that the resulting radiation dose is as low as possible bearing in mind the need to obtain the intended therapeutic result. In each case it must be verified that the risk caused by the radiation is smaller than that of the disease itself.

Exposure to ionizing radiation may increase the risk of cancer and cause hereditary defects.

An administration of $^{32}$P may cause an excessive radiation dose to the red bone marrow, leading to generalized cell deficiency or to other blood dyscrasias which may be fatal. The overall risk is associated with the prognosis of the background illness. According to controlled studies, the incidence of leukemia in patients whose polycythemia vera has been treated with $^{32}$P is 15% at 10 years (7-fold risk to those who have been treated with venesection alone). These cases may prove to be more problematic than conventional treatments. Moreover, there is a 2.5-fold risk of non-hematological malignant illnesses (cancer of the digestive tract and skin). In most cases the acute leukemia was diagnosed 6-10 years after the treatment, but in some cases as early as 2 years after treatment. Therefore radioactive phosphate injection should not be administered to individuals less than 50 years of age.

Chlorambucil treatment is not associated with ionizing radiation, but incidences of malignant illnesses, such as cases of acute leukemia, are associated with this treatment form. On the other hand, when regular venesection is used as the only treatment option, the incidence of malignant diseases remains quite low. However, the incidence of thrombotic complications increases during the first years of treatment.

4.9 Overdose

Since only authorized personnel should administer sodium phosphate ($^{32}$P) in a clinical setting, the likelihood of an overdose is proven to be reduced. An overdose is likely to be limited to an inadvertent administration of excess radioactivity rather than to a small overdose of the chemical substance (the smallest specific activity is 11 MBq/ mg). Excessive radiation will have an effect on all quickly dividing tissues; the effects on the hematological tissues might not manifest themselves until after several months.
Radioactivity to the patient caused by an overdose of $^{32}\text{P}$ should be limited whenever possible by promoting diuresis and frequent voiding of urine. Moreover, the administration of non-labeled phosphate salts might reduce the binding of radionuclides to body tissues and therefore lead to a reduced dose of radiation.

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Therapeutic radioactive medicinal preparations, V10XX01

Small intravenous doses of sodium phosphate are not expected to cause pharmacodynamic effects. Phosphate is one of the most frequently occurring elements in the body (1% of total body weight) and affects the functioning of many tissues (mainly bones, red blood cells and the nervous system). The selective uptake of $^{32}\text{P}$ by the hematological tissues will exert a continuous radiation dose to the dividing cells which will have a significantly detrimental effect on their survival. The uptake of phosphate by different tissues is dependent on several factors, such as the existing amount of tissue phosphate, the amount of new tissue matter and the vascularization of the tissue.

5.2 **Pharmacokinetic properties**

Approximately 10% of the radioactivity of an intravenous dose of sodium phosphate $^{32}\text{P}$ is excreted in the urine within 24 hours, approximately 20% within a week and 46% within two weeks. The glomerulus filters out 90% of the phosphate but 85% thereof is reabsorbed in the renal tubules. A small amount (2%) is detected in the feces (secreted by the intestinal mucosa). Less excretion may occur in patients with extensive neoplasia which involves bones and bone marrow. These are likely to be the patients who have been treated with radioactive phosphate. The biological half-life of $^{32}\text{P}$ is approximately 70% of its physical half-life. Within two weeks approximately 33% of the dose has been distributed within the mineral bones and 20% remains in the internal organs and skeletal muscles. This retention will affect the timing of a repeat treatment. The biological half-life of a dividing bone tissue is over 40 days and, therefore, safety consideration should be associated closely with the physical half-life (14.29 days).

5.3 **Preclinical safety data**

No acute toxicity studies have been carried out with sodium orthophosphate. There are no data on its carcinogenic properties or impact on reproduction.
5.4 Dosimetry

The radiation dose to nontarget organs may be influenced significantly by pathophysiological changes induced by the disease process. This should be taken into consideration when using the following information.

For an administered activity of 555 MBq (indicated only for pain relief in bone metastasis) the typical radiation dose to bone marrow is 6105 mGy and the typical radiation dose to the chest is 511 mGy. (Effective dose equivalent > 1200 mSv/70 kg patient.)

The radiation doses absorbed by various organs are quoted from ICRP publication no. 53 (Vol. 18- No 1-4, 1987). The table shows only the organs used in the calculation of effective dose equivalent. The five organs with the highest radiation doses are marked with *.

Absorbed radiation dose per dose administered (mGy/MBq)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Adult</th>
<th>15 years</th>
<th>10 years</th>
<th>5 years</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals*</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Bladder wall*</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Bone surface*</td>
<td>1.1E+01</td>
<td>1.4E+01</td>
<td>2.3E+01</td>
<td>4.0E+01</td>
<td>9.6E+01</td>
</tr>
<tr>
<td>Breast</td>
<td>9.2E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric wall*</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Small intestine*</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Upper large intestine wall*</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Lower large intestine wall</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Kidneys</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Liver</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Lungs</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Ovaries</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Red bone marrow</td>
<td>1.1E+01</td>
<td>1.5E+01</td>
<td>2.6E-01</td>
<td>5.8E+01</td>
<td>1.2E+02</td>
</tr>
<tr>
<td>Testes</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Thyroid</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Uterus</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Other tissue</td>
<td>7.4E-01</td>
<td>9.2E-01</td>
<td>1.6E+00</td>
<td>2.6E+00</td>
<td>5.4E+00</td>
</tr>
<tr>
<td>Effective dose equivalent</td>
<td>2.2E+00</td>
<td>3.0E+00</td>
<td>5.1E+00</td>
<td>1.0E+01</td>
<td>2.2E+01</td>
</tr>
</tbody>
</table>

(mSv/MBq)
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate
Sodium dihydrogen phosphate
Sodium chloride
Water for injections

6.2 Incompatibilities

None known.

6.3 Shelf life

The product must be used within three weeks of the date of manufacture which is stated on the label.

6.4 Special precautions for storage

The product must be stored at room temperature (15-25 °C) in accordance with regulations for radioactive materials.

6.5 Nature and contents of container

10 ml vial, Type I, closed with a rubber stopper and an aluminum capsule. The volume of the injection solution (5-10 ml) is dependent on the number of doses administered by the operator from the injection solution. The vial is packed in a lead casket. The outer package is a metal canister.

6.6 Instructions for use, handling and disposal

The injection solution is ready for use.

The administration of radiopharmaceuticals may create a radiation risk, and spills of urine, vomit, etc. may cause a contamination risk to other persons. Radiation protection precautions in accordance with regulations must therefore be taken.

Ampoules and syringes can be disposed of as normal community waste, unless their radioactivity exceeds the allowed limits as measured with a radiation counter. Waste must be disposed of in accordance with regulations.
7. MARKETING AUTHORIZATION HOLDER

MAP Medical Technologies Oy
Elementtitie 27
FIN-41160 Tikkakoski, Finland

8. MARKETING AUTHORIZATION NUMBER

11303

9. DATE OF FIRST AUTHORIZATION

November 29, 1993

10. DATE OF REVISION OF THE TEXT

April 15, 2002