SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ItraPol, radiopharmaceutical precursor, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 0.925-37 GBq Yttrium (^{90}Y) on the reference date and time (corresponding to 46-1840 nanograms of Yttrium [^{90}Y]) in a volume 0.010-2 ml as Yttrium [^{90}Y] chloride in a diluted hydrochloric acid.
Yttrium (^{90}Y) chloride is produced by decay of its radioactive precursor Strontium (^{90}Sr). It decays by emission of beta radiation with maximum energy 2.281 MeV (99.98%), to stable Zirconium (^{90}Zr).
Yttrium (^{90}Y) has a half-life of 2.67 days (64.1 hours).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Radiopharmaceutical precursor, solution.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To be used only for the radiolabelling of medicinal products, which have been specifically developed and authorised for radiolabelling with this radionuclide.
Radiopharmaceutical precursor - not intended for direct use in patients.

4.2 Posology and method of administration

Posology

The quantity of ItraPol required for radiolabelling and the quantity of Yttrium (^{90}Y)-labelled medicinal product that is subsequently administered will depend on the medicinal product radiolabelled and its intended use. Refer to the Summary of Product Characteristics/Package leaflet of the particular medicinal product to be radiolabelled.

Method of administration

ItraPol is intended for *in vitro* labelling of medicinal products which are subsequently administered by the approved route.
Further information on the preparation of the product is given in section 12.

4.3 Contraindications

Do not administer ItraPol directly to the patient.
ItraPol is contraindicated in the following cases:
- Hypersensitivity to Yttrium (^{90}Y) chloride or to any of the excipients listed in section 6.1

Yttrium (^{90}Y)-labelled medicinal products are contraindicated in the following cases:
- Established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6)
- Breastfeeding

For information on contraindications to particular Yttrium (^{90}Y)-labelled medicinal products prepared by radiolabelling with ItraPol refer the Summary of Product Characteristics/Package leaflet of the particular medicinal product to be radiolabelled.

4.4 Special warnings and precautions for use

The contents of the vial of ItraPol is not to be administered directly to the patient but must be used for the radiolabelling of carrier molecules, such as monoclonal antibodies, peptides or other substrates.
For each patient, the radiation exposure must be justifiable by the likely benefit from the therapeutic procedure with use of this radiopharmaceutical. The quantity of ItraPol required for radiolabelling and the quantity of Yttrium (^{90}Y)-labelled medicinal product that is subsequently administered, should in every case be as low as reasonably achievable to obtain the required therapeutic effect.
For information concerning special warnings and special precautions for use of Yttrium (90Y)-labelled medicinal products refer to the Summary of Product Characteristics/Package leaflet of the medicinal product to be radiolabelled.

Paediatric population

Particular care should be taken when administering radioactive medicinal products to children and adolescents (from 2 to 16 years old).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies of Yttrium (^{90}Y) chloride with other medicinal products have been performed, because ItraPol is a precursor solution for radiolabelling of medicinal products.
For information concerning interactions associated with the use of Yttrium (^{90}Y)-labelled medicinal products refer to the Summary of Product Characteristics/ Package leaflet of the medicinal product to be radiolabelled.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during and in a short period after treatment.
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy

Yttrium (^{90}Y)-labelled medicinal products are contraindicated in established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3).

Breastfeeding

Before administering Yttrium (^{90}Y)-labelled medicinal products to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding. If the administration is considered necessary, breastfeeding should be stopped.
Further information concerning the use of a Yttrium (^{90}Y)-labelled medicinal products in pregnancy and breastfeeding is specified in the Summary of Product Characteristics/Package leaflet of the medicinal product to be radiolabelled.

Fertility

Information about use of a Yttrium (^{90}Y)-labelled medicinal products concerning fertility is specified in the Summary of Product Characteristics of the medicinal product to be radiolabelled.

4.7 Effects on ability to drive and use machines

Effects on ability to drive and to use machines following treatment by Yttrium (^{90}Y)-labelled medicinal products will be specified in the Summary of Product Characteristics/Package leaflet of the medicinal product to be radiolabelled.

4.8 Undesirable effects

Possible adverse reactions following the intravenous administration of a Yttrium (^{90}Y)-labelled medicinal product prepared by radiolabelling with ItraPol, will be dependent on the specific medicinal product being used. Such information will be specified in the Summary of Product Characteristics/Package leaflet of the medicinal product to be radiolabelled.
For each patient, exposure to ionising radiation must be justifiable on the basis of likely clinical benefit. The activity administered, should in every case be as low as reasonably achievable to obtain the required therapeutic effect.
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.
The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases, it is necessary to ensure that the risks of the radiation are less than from the disease itself.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. Adverse reactions may be reported to Marketing Authorisation Holder.

4.9 Overdose

The presence of free Yttrium (^{90}Y) chloride in the body after an inadvertent administration of ItraPol will lead to increased bone marrow toxicity and haematopoietic stem cell damage.
Therefore, in case of an inadvertent administration of ItraPol, the radioactivity in the patient body must be reduced by immediate (i. e. within 1 hour) administration of preparations containing chelators like Ca-DTPA or Ca-EDTA in order to increase the elimination of the radionuclide from the body.
The following preparations must be available in medical institutions, which use ItraPol for labelling of carrier molecules for therapeutic purposes:
- Ca-DTPA (Trisodium calcium diethylenetriaminepentaacetate) or
- Ca-EDTA (Calcium disodium ethylenediaminetetraacetate)

These chelating agents suppress yttrium radiotoxicity by an exchange between the calcium ion and the yttrium due to their capacity of forming water soluble complexes with the chelating ligands (DTPA, EDTA). These complexes are rapidly eliminated by the kidneys.
1 g of the chelating agents should be administered by slow intravenous injection over 3–4 minutes or by infusion (1 g in 100–250 ml of glucose, or normal saline). The chelating efficacy is greatest immediately or within one hour of exposure when the radionuclide is circulating in or available to tissue fluids and plasma. However, a post-exposure interval > 1 hour does not preclude the administration and effective action of chelator with reduced efficiency. Intravenous administration should not be protracted over more than 2 hours.
In any case the blood parameters of the patient have to be monitored and the appropriate actions immediately taken if there is evidence of damage to the blood marrow.
The toxicity of the free Yttrium (^{90}Y) due to *in vivo* release from the labelled biomolecule into the body during therapy could be reduced by post-administration of chelating agents.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals, ATC code: V10X.
The pharmacodynamic properties of Yttrium (^{90}Y)-labelled medicinal products prepared by radiolabelling with ItraPol, prior to administration, will be dependent

on the nature of the medicinal product to be radiolabelled. Refer to the Summary of Product Characteristics/Package leaflet of the particular medicinal product to be radiolabelled.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of Yttrium (^{90}Y)-labelled medicinal products prepared by radiolabelling with ItraPol, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled.

In the rat, following intravenous administration, Yttrium (^{90}Y) chloride is rapidly cleared from the blood. At 1 and 24 hours, blood radioactivity decreases from 11.0% to 0.14% of the administered activity. The two main organs where Yttrium (^{90}Y) chloride distributes are the liver and bones. In the liver, 18% of the injected activity is taken up 5 min after injection. Liver uptake decreases then to 8.4% 24 hours after injection. In bone, percentage of injected activity increases from 3.1% at 5 min to 18% at 6 hours and then decreases with time. Faecal and urinary elimination is slow: about 13% of the administered activity is eliminated in 15 days.

5.3 Preclinical safety data

The toxicological properties of Yttrium (^{90}Y)-labelled medicinal products prepared by radiolabelling with ItraPol prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled.

There are no data available on the toxicity of Yttrium (^{90}Y) chloride nor on its effects on reproduction in animals or its mutagenic or carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (concentrated)
Water for injections

6.2 Incompatibilities

Radiolabelling of medicinal products, such as monoclonal antibodies, peptides or other substrates, with Yttrium (^{90}Y) chloride is very sensitive to the presence of trace metal impurities. It is important that all materials used for the preparation of the radiolabelled medicinal product are thoroughly cleaned to ensure freedom from such trace metal impurities. Needles (for example, non-metallic) with proven resistance to dilute acid should only be used to minimise trace metal impurity levels.

6.3 Shelf life

7 days from the date of manufacture.

6.4 Special precautions for storage

Store below 25°C.
Store in the original package.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

Colourless type I glass vial of 2 ml volume closed with a rubber stopper and aluminium seal, placed in a shielding lead container.
Pack size: 1 vial
During storage, due to ionising radiation, the vial may change color into yellow-brown. This discoloration has no influence into the product quality.

6.6 Special precautions for disposal

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Contents of the vial are intended only for use after radiolabelling of medicinal products, which have been specifically developed and authorised for radiolabelling with this radionuclide, and are not to be administered directly to the patient without first undergoing the preparative procedure.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

22069

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08.09.2014

10. DATE OF REVISION OF THE TEXT

08.09.2014

11. DOSIMETRY

The radiation dose absorbed by the various organs following intravenous administration of an Yttrium (^{90}Y)-labelled medicinal product is dependent on the specific medicinal product being radiolabelled. Information on radiation dosimetry following administration of Yttrium (^{90}Y)-labelled medicinal product will be available in the Summary of Product Characteristics/Package leaflet of the particular medicinal product to be radiolabelled.

The dosimetry table below is presented in order to evaluate the contribution of non-conjugated Yttrium (^{90}Y) to the radiation dose following the administration of Yttrium (^{90}Y)-labelled medicinal product or resulting from an accidental intravenous injection of radiopharmaceutical precursor.

The dosimetry estimates were based on a rat distribution study and the calculations were effected in accordance with MIRD/ICRP 60 recommendations.

Absorbed dose per unit activity administered [mGy/MBq]						
Organ	**Adult (70 kg)**	**15 years (50 kg)**	**10 years (30 kg)**	**5 years (17 kg)**	**1 year (10 kg)**	**Newborn (5 kg)**
Adrenals	0.723	1.090	2.530	3.620	7.230	21.700
Blood	0.042	0.0629	0.147	0.210	0.419	1.260
Bone marrow	2.580	3.880	9.050	12.90	25.80	77.500
Brain	0.0086	0.0129	0.0301	0.043	0.0860	0.258
Carcass	0.582	0.872	2.040	2.910	5.820	17.500
Colon	0.023	0.0346	0.0806	0.115	0.230	0.691
Femur	7.760	11.60	27.20	38.80	77.60	233.00
Heart	0.253	0.379	0.885	1.260	2.530	7.590
Ileum	0.0116	0.0174	0.0406	0.0581	0.116	0.348
Kidneys	2.350	3.530	8.240	11.80	23.50	70.600
Liver	1.270	1.910	4.460	6.370	12.70	38.200
Lungs	0.423	0.634	1.480	2.110	4.230	12.700
Ovaries	0.333	0.499	1.170	1.660	3.330	9.990
Pancreas	0.079	0.118	0.276	0.395	0.790	2.370
Skeletal muscle	0.000612	0.000917	0.00214	0.00306	0.00612	0.0183
Skin	0.102	0.153	0.358	0.511	1.020	3.060
Spleen	0.490	0.736	1.720	2.450	4.900	14.700
Stomach	0.0647	0.0970	0.226	0.323	0.647	1.940
Thymus	0.0734	0.110	0.257	0.367	0.734	2.200
Thyroid	0.999	1.500	3.500	5.000	9.990	30.000
Urinary bladder	0.362	0.544	1.270	1.810	3.620	10.900
Uterus	0.0151	0.0226	0.0528	0.0755	0.151	0.453
Effective dose [mSv/MBq]	**0.665**	**0.998**	**2.330**	**3.330**	**6.650**	**19.900**

For this product the effective dose to a 70 kg adult resulting from an intravenously injected activity of 1 GBq is 665 mSv.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Before use, packaging and radioactivity should be checked. Activity may be measured using an ionisation chamber. Yttrium (^{90}Y) is a beta pure emitter. Activity measurements using an ionisation chamber are very sensitive to geometric factors and, therefore, should be performed only under geometric conditions which have been appropriately validated.

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

The vial should never be opened and must be kept inside its lead shielding. The product should be aseptically withdrawn via the stopper using sterilised disposable needle and syringe, after disinfecting the stopper.

Before withdrawal the product can be diluted with the solution recommended in the labelling procedure of the product to be radiolabelled.

Appropriate aseptic precautions should be taken complying with radiation safety and pharmaceutical quality requirements, in order to maintain the product and labelling procedure sterility.

Any unused product or waste material should be disposed of in accordance with local requirements.

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