PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

YTTRIGA™

Yttrium (^{90}Y) chloride

Radiopharmaceutical precursor, sterile solution.

Manufactured by:
Eckert & Ziegler Radiopharma GmbH
Robert-Rössle-Strasse 10
Berlin, 13125
Germany

Imported and distributed by:
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RECENT MAJOR LABEL CHANGES

Not Applicable.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

YTTRIGA™ is a radiopharmaceutical precursor intended for use in the preparation of radiolabelled monoclonal antibodies. It is not intended for direct use in patients (see Dosage and Administration).

1.1 Pediatrics

Not intended for direct use.

1.2 Geriatrics

Not intended for direct use.

2 CONTRAINDICATIONS

Do not administer YTTRIGA™ directly to the patient.

Yttrium (^{90}Y)-labelled medicinal products are contraindicated in the following cases:

- Established or suspected pregnancy or when pregnancy has not been excluded, and breast feeding (see WARNINGS & PRECAUTIONS).
- In patients who are hypersensitive to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging of radiolabelled products.

For information on contraindications to particular Yttrium (^{90}Y)-labelled medicinal products prepared by radiolabelling with YTTRIGA™ refer the Product Monograph or Package Insert of the particular medicinal product to be radiolabelled.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in humans.
- Do not administer YTTRIGA™ directly to the patient.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

YTTRIGA™ is intended for in vitro labelling of medicinal products which are subsequently administered by the approved route.

4.2 Dosage

The quantity of YTTRIGA™ required for radiolabelling and the quantity of Yttrium (^{90}Y)-labelled medicinal product will depend on the medicinal product radiolabelled and its intended use. Refer to the Product Monograph or Package Insert of the particular medicinal product to be radiolabelled.

Administration
The patient dose should be measured by a suitable radioactivity calibration system prior to administration.

Do not administer YTTRIGA™ directly to the patient.

4.3 Image Acquisition and Interpretation

Not applicable

4.4 Instructions for Preparation and Use

Before use, integrity and radioactivity should be checked. Activity may be measured using an ionisation chamber or other dosimeters for pure beta emitters. 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.

Use aseptic technique and wear waterproof gloves throughout the entire preparation procedure.

Make all transfers of radioactive solutions with an adequately shielded syringe and maintain adequate shielding around the vial during the useful life of the radioactive product.

Do not use if the solution contains particulate matter or is not a clear solution.

4.5 Directions for Quality Control

The appearance, pH and radiochemical purity of YTTRIGA™ should be determined.
For detailed Quality Control procedure, please follow the instructions given in the Product Monograph of the medicinal product that is to be radiolabelled with YTTRIGA™.

Appearance: Clear and colourless
Radiochemical purity: > 99 %

5 RADIATION DOSIMETRY

The radiation dose received 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 of each different medicinal product following administration of the radiolabelled preparation will be available in the Product Monograph or Package Insert of the particular medicinal product to be radiolabelled.

The dosimetry of YTTRIGA™ from humans is not available. The dosimetry table below from rodents is presented in order to evaluate the contribution of absorbed dose from non-conjugated Yttrium (^{90}Y) following the administration of Yttrium (^{90}Y)-labelled medicinal product or resulting from an accidental intravenous injection of YTTRIGA™.

The dosimetry estimates were based on a rat distribution study and the calculations were effected in accordance with MIRD/ICRP 60 recommendations. Time-points for measurements were 5 min, 1, 6, 24, 96 and 360 hours.

Table 1- Absorbed dose per unit activity administered (mGy/MBq)

Organ
Adrenals
Blood
Bone marrow
Brain
Carcass
Colon
Femur
Gastro-intestinal content
Heart
Ileum
Kidneys
Liver
Lungs
Ovaries
Pancreas
Skeletal muscle
Skin
Spleen
Stomach
Thymus
Thyroids
Urinary bladder
Uterus
Effective Dose (mSv/MBq)

The estimated effective dose to a 70 kg adult resulting from an intravenously injected activity of 1.0 GBq of Yttrium (^{90}Y) chloride is 665 mSv.

6 OVERDOSAGE

The presence of free Yttrium (^{90}Y) chloride in the body after an inadvertent administration of YTTRIGA™ will lead to increased bone marrow toxicity and haematopoietic stern cell damage. Therefore, in case of an inadvertent administration of Yttriga, the radiotoxicity for the patient 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 YTTRIGA™ 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 dextrose, 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 bone marrow.

The toxicity of the free Yttrium (^{90}Y) due to in-vivo release from the labelled biomolecule in the body during therapy could be reduced by post-administration of chelating agents.

For management of a suspected drug overdose, contact your regional poison control centre.

7 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
YTTRIGA™ is intended for in vitro labelling of medicinal products which are subsequently administered by the approved route.	Clear colourless sterile solution in colourless glass vial (type I) of 3 ml with a V-shaped bottom with a silicon stopper, closed with an aluminium seal / 0.1-300 GBq Yttrium (90Y)*	Hydrochloric acid (0.04 M)

*corresponding to 0.005-15 micrograms of Yttrium (^{90}Y) (as Yttrium (^{90}Y) chloride) on the reference date and time

8 DESCRIPTION

Physical Characteristics

Yttrium (^{90}Y) chloride is produced by decay of its radioactive precursor Strontium (^{90}Sr). It decays by emission of beta radiation of 2.281 MeV (99.98 %) of maximal energy, with a mean energy of 934 KeV, to stable Zirconium (^{90}Zr). Yttrium (^{90}Y) has a half-life of 2.67 days (64.1 hours).
The maximum range of beta particles in soft tissue is 12 mm and the mean range is 2.5 mm.

External Radiation
The exposure rate for 37 MBq (1 mCi) of ^{90}Y is 8.3 x 10-3 Ci/kg/hr (32 R/hr) at the mouth of an open ^{90}Y vial. Adequate shielding should be used with this beta emitter, in accordance with institutional good radiation safety practices.

To allow correction for physical decay of ^{90}Y, the fractions that remain at selected intervals before and after the time of calibration are shown below.

Table 3 – Physical Decay Chart: 90Y Half-Life 2.67 Days (64.1 Hours)

Calibration Time (Hrs.)	Fraction Remaining	Calibration Time (Hrs.)	Fraction Remaining
-36	1. 48	0	1.00
-24	1.30	1	0.99
-12	1.14	2	0.98
-8	1.09	3	0.97
-7	1.08	4	0.96
-6	1.07	5	0.95
-5	1.06	6	0.94
-4	1.04	7	0.93
-3	1.03	8	0.92
-2	1.02	12	0.88
-1	1.01	24	0.77
0	1.00	36	0.68

9 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

Do not administer YTTRIGA™ directly to the patient.

The labelled product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The radiopharmaceutical product should be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation

exposure to occupational workers.

Carcinogenesis and Mutagenesis
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; however, the radiation dose resulting from therapeutic exposure to Yttrium (^{90}Y) radiolabeled medicinal products may result in secondary malignancies.

Contamination
The administration of radioactive medicinal products creates risks for other persons from external radiation or contamination from spills of feces, urine, vomiting, etc. To minimize any potential radiation exposure to other people, patients should be cautioned to avoid the transfer of bodily fluids:

- Safety precautions to be followed for 7 days: Wash hands thoroughly after using the bathroom; use condoms during sexual intercourse to avoid transfer of bodily fluids.

Hematologic
The presence of free Yttrium (^{90}Y) chloride in the body after an inadvertent administration of YTTRIGA™ will lead to increased bone marrow toxicity and haematopoietic stern cell damage (See OVERDOSAGE).

Sexual Health
Reproduction
Women of childbearing potential have to use effective contraception during and after treatment.

Fertility
Information concerning the use of Yttrium (^{90}Y)-labelled medicinal product on fertility is specified in the Product Monograph or Package Insert of the medicinal product to be radiolabelled.

9.1 Special Populations

9.1.1 Pregnant Women

Yttrium (^{90}Y)-labelled medicinal product is contraindicated in established or suspected pregnancy or when pregnancy has not been excluded (see CONTRAINDICATIONS).

9.1.2 Breast-feeding

Before administering a radioactive medicinal product to a mother who is breast-feeding, consideration should be given to whether the treatment could be reasonably delayed until the mother has ceased breast-feeding. If the administration cannot be delayed, a lactating mother should be advised to stop breast-feeding.

9.1.3 Pediatrics

Pediatrics (**<18 years of age)**: No data are available.

9.1.4 Geriatrics

No data are available.

10 ADVERSE REACTIONS

10.1 Adverse Reaction Overview

Possible adverse reactions following the intravenous administration of Yttrium (^{90}Y)-labelled medicinal product will be dependent on the specific medicinal product being used. Such information will be supplied in the Product Monograph or Package Insert of the medicinal product to be radiolabelled.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.

The radiation exposure from radioactive therapy may result in higher incidence of cancer and mutations.
For each patient, exposure to ionising radiation must be justifiable on the basis of likely clinical benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended therapeutic result.

10.2 Clinical Trial Adverse Reactions - Not applicable

10.3 Less Common Clinical Trial Adverse Reactions - Not applicable

10.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data - Not applicable

10.5 Clinical Trial Adverse Reactions (Pediatrics) - Not applicable

10.6 Post-Market Adverse Reactions - Not applicable

11 DRUG INTERACTIONS

11.1 Drug-Drug Interactions

No interaction studies of Yttrium (^{90}Y) chloride with other medicinal products have been performed, because YTTRIGA™ is a precursor solution for radiolabelling medicinal products.

For information concerning interactions associated with the use of Yttrium (^{90}Y)-labelled medicinal

products refer to the Product Monograph or Package Insert of the medicinal product to be radiolabelled.

11.2 Drug-Food Interactions

Interactions with food have not been established.

11.3 Drug-Herb Interactions

Interactions with herbs have not been established.

11.4 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

11.5 Drug-Lifestyle Interactions

Interactions with lifestyles have not been established.

12 ACTION AND CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Yttrium (^{90}Y) Chloride Sterile Solution is a radiopharmaceutical precursor and to be used only by specialists experienced with in vitro radiolabelling of monoclonal antibodies. Refer to the Product Monograph or Package Insert of the particular medicinal product to be radiolabelled.

12.2 Pharmacodynamics

The pharmacodynamic properties of Yttrium (^{90}Y)-labelled medicinal products prepared by radiolabelling with YTTRIGA™, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled. Refer to the Product Monograph or Package Insert of the particular medicinal product to be radiolabelled.

12.3 Pharmacokinetics

The pharmacokinetic properties of Yttrium (^{90}Y)-labelled medicinal products prepared by radiolabelling with YTTRIGA™, 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 31 % of the administered activity is eliminated in 15 days.

13 STORAGE, STABILITY AND DISPOSAL

YTTRIGA™ sterile solution is to be stored at 15°C-30°C.

YTTRIGA™ sterile solution expires within 12 days after production (maximum of 9 days of pre-calibration and an additional 3 days of application time after the calibration date). Do not use after the expiry date printed on the package.

14 SPECIAL HANDLING INSTRUCTIONS

The vial may contain high pressure due to radiolysis.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

PART II: SCIENTIFIC INFORMATION

15 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Yttrium-90

Chemical name: Yttrium-90

Molecular formula and molecular mass: Y, 89.907 g/mol

Structural formula: Y

Product Characteristics

Radiopharmaceutical precursor, solution. Clear colourless solution, free of particles.

16 CLINICAL TRIALS

For information on clinical trials conducted with Yttrium (^{90}Y)-labelled medicinal products prepared, refer to the Product Monograph or Package Insert of the particular medicinal product to be radiolabelled.

17 NON-CLINICAL TOXICOLOGY

The toxicological properties of Yttrium (^{90}Y)-labelled medicinal products prepared by radiolabelling with YTTRIGA™ 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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

YTTRIGA™

Yttrium (^{90}Y) chloride

Radiopharmaceutical precursor, sterile solution.

Read this carefully before you start taking YTTRIGA™ labelled product. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about YTTRIGA™.

Serious Warnings and Precautions

- **Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in humans.**
- **YTTRIGA™ is not intended for direct use in patients.**

What is YTTRIGA™ used for?

YTTRIGA™ contains Yttrium-90 (^{90}Y), a radioisotope. A radioisotope is an atom that gives off energy in the form of a certain type of radiation. YTTRIGA™ is used in combination with other medicines which target specific body cells. When the target is reached, YTTRIGA™ gives tiny radiation doses to these specific sites. YTTRIGA™ is not intended for direct use in patients.

How does YTTRIGA™ work?

When YTTRIGA™ is combined with another medicine, that product is said to be radiolabeled. Within the body, the energy given off by Yttrium-90 has certain therapeutic benefits which depend on the type of product with which YTTRIGA™ is combined. For further information regarding the radiolabelled medicinal product, please refer to the package leaflet of that product.

What are the ingredients in YTTRIGA™?

Medicinal ingredients: Yttrium-90 chloride
Non-medicinal ingredients: Hydrochloric acid

YTTRIGA™ comes in the following dosage forms:

YTTRIGA™ is provided in glass vials containing sterile solution.

Do not use YTTRIGA™:

- If you have an allergy (if you are hypersensitive) to the active ingredient to yttrium chloride, or any other component of the product.
- If you are pregnant or if there is a possibility that you may be pregnant.
- If you are nursing

Other warnings you should know about:

Please refer to the Patient Leaflet of the therapeutic product which has been radiolabeled with YTTRIGA™ for other warnings you should know about.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with YTTRIGA™:

- Interactions with YTTRIGA™ have not been assessed. Please refer to the Patient Leaflet of the therapeutic product which has been radiolabeled with YTTRIGA™ for other potential interactions you should know about.

How to take YTTRIGA™:
YTTRIGA™ is not intended for direct use. It will be handled by healthcare professionals who are trained and qualified in the safe handling of radioactive material..

Usual dose:
The dose of the product labelled with YTTRIGA™ will be determined by your healthcare professional.

Overdose:
YTTRIGA™ is administered after being combined with another medicine by your doctor under strictly controlled conditions. The risk of receiving a possible overdose is small. In the case of inadvertent event, the excessive radiation may lead to increased bone marrow toxicity and damage to certain types of blood cells. Please refer to the Patient Leaflet of the therapeutic product which has been radiolabeled with YTTRIGA™ for additional information on overdosage.

What are possible side effects from using YTTRIGA™?
Like all medicines, YTTRIGA™ can cause side effects, although not everybody gets them. For more information, refer to the Patient Leaflet of the particular medicinal product to be radiolabelled.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. These are not all the possible side effects you may feel when taking YTTRIGA™ labelled product. If you experience any side effects not listed, contact your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE Bone marrow toxicity and haematopoietic stern cell damage (due to adventitious injection or overdose)		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about YTTRIGA™:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.servier.ca , or by calling 1-800-363-6093

This leaflet was prepared by Eckert & Ziegler Radiopharma GmbH.

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