ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

YTRACIS radiopharmaceutical precursor, solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of sterile solution contains 1.850 GBq Yttrium (^{90}Y) chloride, at the date of calibration, corresponding to 92 ng of Yttrium.

One vial contains 0.925 to 3.700 GBq (see section 6.5).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Radiopharmaceutical precursor, solution.

Clear, colourless solution, free of particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To be used only for the radiolabelling of carrier molecules which have been specifically developed and authorised for radiolabelling with this radionuclide.

Radiopharmaceutical precursor - Not intended for direct application to patients.

4.2 Posology and method of administration

YTRACIS is only to be used by specialists with the appropriate experience.

The quantity of YTRACIS 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.

YTRACIS is intended for *in vitro* radiolabelling of medicinal products, which are subsequently administered by approved route.

4.3 Contraindications

Do not administer YTRACIS directly to the patient.
YTRACIS is contraindicated in the following cases:
- Hypersensitivity to the active substance or to any of the excipients.
- Established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6).

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

4.4 Special warnings and precautions for use

The content of the vial of YTRACIS 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.

Radioactive medicinal products should be received, used and administered only by authorised persons in designated clinical settings and receipt, storage, use, transfer and disposal are subject to the regulations and appropriate licences of the competent authorities.

Radioactive medicinal products should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements.

For information concerning special warnings and precautions for use of Yttrium (^{90}Y)-labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

Particular care should be taken when administering radioactive medicinal products to children and adolescents.

4.5 Interactions with other medicinal products and other forms of interaction

No interaction studies have been performed.

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 Pregnancy and lactation

YTRACIS is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3 Contraindications).

When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Alternative techniques which do not involve ionising radiation should always be considered.

Radionuclide procedures carried out in pregnant women also involve radiation doses to the foetus.
The absorbed dose to the uterus following administration of Yttrium (^{90}Y)-labelled medicinal products is dependent on the specific medicinal product being radiolabelled and is to be specified in the Summary of Product Characteristics/ package leaflet of the medicinal product to be radiolabelled.

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

For information concerning the use of Yttrium (^{90}Y)-labelled medicinal products in pregnancy and lactation refer to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.

4.7 Effects on ability to drive or use machines

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable Effects

Possible side effects following the intravenous administration of Yttrium (^{90}Y)-labelled medicinal products prepared by radiolabelling with YTRACIS, will be dependent on the specific medicinal product being used. Such information will be supplied 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 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.

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

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 listed in Appendix V.

4.9 Overdose

The presence of free Yttrium (^{90}Y) chloride in the body after an inadvertent administration of Ytracis will lead to increase bone marrow toxicity and haematopoetic stem cell damage. Therefore, in case of an inadvertent administration of Ytracis, 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 Ytracis for radiolabelling 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 blood 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not applicable
ATC code: Not applicable

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 to stable Zirconium (^{90}Zr). ^{90}Y-yttrium has a half-life of 2.67 days (64.1 hours).

The pharmacodynamic properties of Yttrium (^{90}Y)-labelled medicinal products prepared by radiolabelling with YTRACIS, 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 YTRACIS, 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 % 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 YTRACIS 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 30 %
Water for injections

6.2 Incompatibilities

Radiolabelling of carrier molecules, 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 glassware, syringe needles etc, used for the preparation of the radiolabelled medicinal product are thoroughly cleaned to ensure freedom from such trace metal impurities. Only syringe needles (for example non-metallic) with proven resistance to dilute acid should be used to minimise trace metal impurity levels.

6.3 Shelf life

7 days from the date/hour of manufacture.

6.4 Special precautions for storage

Store in the original package.

Storage should be in accordance with local regulations for radioactive substances.

6.5 Nature and contents of container

Colourless Type I glass 2-ml vial, closed with Teflon-coated bromobutyl rubber stopper and aluminium overseal.

1 vial contains 0.5 to 2 ml (corresponding to 0.925 to 3.700 GBq calibrated three or four days after the manufacturing date) depending on the ordered radioactivity.

The vial is supplied in a lead pot of appropriate thickness.

6.6 Special precautions for disposal and other handling

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

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

See section 12, for detailed instructions of product preparation.

7. MARKETING AUTHORISATION HOLDER

CIS bio international
Boîte Postale 32
F-91192 GIF-SUR-YVETTE CEDEX
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/250/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the first authorisation: 24/03/2003
Date of the last renewal: 24/03/2008

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

The radiation dose received by the various organs following administration of a Yttrium (^{90}Y)-labelled medicinal product will be dependent on the specific pharmaceutical being radiolabelled. Information on radiation dosimetry of each different medicinal product following administration of the radiolabelled preparation 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 YTRACIS.

The dosimetry estimates were based on a rat biodistribution study and the calculations were effected in accordance with MIRD/ICRP 60 recommendations. Timepoints for measurements were 5 minutes, 1 hour, 6 hours, 1 day, 4 days and 15 days.

Organ doses (mGy/MBq injected) and effective dose (Sv/GBq injected).

Absorbed dose per unit activity administered (mGy/MBq)							
Organ	**Adult male 70 kg**	**Adult female 57 kg**	**15 years**	**10 years**	**5 years**	**1 year**	**New Born**
Kidneys	5.06	5.50	6.10	8.75	13.0	24.1	66.1
Liver	2.41	3.29	3.29	5.20	7.89	15.8	38.1
Bladder	2.11	2.78	2.78	4.31	6.87	13.5	35.8
Ovaries	---	0.88	0.92	3.1	5.6	13.6	29.6
Uterus	---	0.29	0.3	5.7	8.8	16.3	6.15
Spleen	0.85	1.04	1.27	2.02	3.23	6.12	17.1
Bone	0.30	0.29	0.29	0.53	0.98	1.37	2.41
Heart	0.26	0.33	0.34	0.54	0.87	1.60	3.18
Lungs	0.11	0.14	0.17	0.24	0.37	0.75	2.13
Intestines	0.10	0.11	0.13	0.23	0.39	0.78	2.02
Muscles	0.05	0.08	0.09	0.20	0.68	1.36	1.79
Testes	0.01	---	0.03	0.23	0.26	0.36	0.51
Effective dose (Sv/1 GBq administered)							
	Adult male	**Adult female**	**15 years**	**10 years**	**5 years**	**1 year**	**New Born**
	0.65	**0.70**	**0.74**	**1.50**	**2.50**	**5.42**	**12.8**

For this product, the effective dose resulting from an intravenously injected activity of 1 GBq is 700 mSv for a 57-kg female adult and 650 mSv for a 70-kg male adult.

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.
Usual precautions regarding sterility and radioactivity should be respected.

The vial should never be opened and must be kept inside its lead shielding. The product should be aseptically withdrawn through the stopper using sterilised single use needle and syringe after disinfection of the stopper.
Appropriate aseptic precautions should be taken, complying with the requirements of Good Pharmaceutical Manufacturing Practice, in order to maintain the sterility of YTRACIS and to maintain sterility throughout the labelling procedures.

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

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

CIS bio international
Boîte Postale 32
91192 GIF-SUR-YVETTE Cedex
France

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 7 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A.LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

METALLIC BOX / LEAD POT

1. NAME OF THE MEDICINAL PRODUCT

YTRACIS Radiopharmaceutical precursor, solution.
Yttrium (^{90}Y) chloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Yttrium (^{90}Y) chloride 1.850 GBq/ml

3. LIST OF EXCIPIENTS

Hydrochloric acid 30%, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Radiopharmaceutical precursor, solution.

1 vial
Vol.: {Z} ml
Act.: {Y} GBq/vial Cal : {DD/MM/YYYY} (12 h CET)
Act.: {Y} GBq/ml Cal: {DD/MM/YYYY} (12 h CET)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

NOT INTENDED FOR DIRECT APPLICATION TO PATIENTS.
For *in vitro* radiolabelling. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {DD/MM/YYYY} (12h CET)

9. SPECIAL STORAGE CONDITIONS

Store in the original package.

Storage should be in accordance with local regulations for radioactive substances.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CIS bio international
BP 32
F-91192 GIF-SUR-YVETTE Cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/250/001

13. BATCH NUMBER

Batch N°: {XXXXX}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medical product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

GLASS VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

YTRACIS Yttrium (^{90}Y) chloride

2. METHOD OF ADMINISTRATION

For *in vitro* radiolabelling.
NOT INTENDED FOR DIRECT APPLICATION TO PATIENTS

3. EXPIRY DATE

EXP {DD/MM/YYYY} (12h CET)

4. BATCH NUMBER

Batch: {XXXXX}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Vol.: {Z} ml

Act.: {Y}_____GBq/vial Cal.: {DD/MM/AAAA} (12h CET)

6. OTHER

B.PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

YTRACIS radiopharmaceutical precursor, solution.
Yttrium (^{90}Y) chloride.

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- 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. See section 4.

In this leaflet:

1. WHAT YTRACIS IS AND WHAT IT IS USED FOR

YTRACIS is a radioactive medicine used in combination with another medicine product which targets specific body cells. When the target is reached, Ytracis gives tiny radiation doses to these specific sites.

For further information regarding the treatment and possible effects caused by the medicinal product to be radiolabelled please refer to the package leaflet of the medicinal product to be radiolabelled.

2. BEFORE YOU USE YTRACIS

Do not use YTRACIS:
- if you are hypersensitive (allergic) to Yttrium (^{90}Y) chloride or any of the other ingredients of YTRACIS.
- if you are pregnant or if there is a possibility that you might be pregnant (see below).

Take special care with YTRACIS:
YTRACIS is not to be administered directly to the patient.

Because there are strict laws covering the use, handling and disposal of radioactivity, YTRACIS will always be used in a hospital or a similar setting. It will only be handled and administered by people who are trained and qualified in the safe handling of radioactive material.

Particular care should be taken when administering radioactive medicinal products to children and adolescents.

Pregnancy:
Ask your doctor or pharmacist for advice before taking any medicine.

It is important to tell your doctor if there is any possibility that you are pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Alternative techniques which do not involve radioactive medicines should always be considered.

Breast-feeding:
Ask your doctor or pharmacist for advice before taking any medicine.

You will be asked to stop breast-feeding.

Driving and using machines:
No studies on the effects on the ability to drive and use machines have been performed.

Taking other medicines:
No interactions of Yttrium (^{90}Y) chloride with other medicinal products are known because no studies have investigated this issue.
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

3. HOW TO USE YTRACIS

YTRACIS is not to be administered directly to the patient.

Dosage
Your physician will decide on the amount of YTRACIS to be used in your case.

Method of Administration
YTRACIS is intended for radiolabelling of medicinal products to treat specific diseases, which are subsequently administered by approved route.

If you use more YTRACIS than you should
Since YTRACIS is administered by a doctor under strictly controlled conditions there is little chance of possible overdose. However, should this occur, you will receive appropriate treatment from your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, YTRACIS can cause side effects, although not everybody gets them.

For more information, refer to the package leaflet of the particular medicinal product to be radiolabelled.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE YTRACIS

Keep out of the reach and sight of children.
Do not use after the expiry date and time stated on the label.
Store in the original package.
Store in accordance with local regulations for radioactive substances.

The product label includes the appropriate storage conditions and the expiry date for the batch of product. Hospital personnel will ensure that the product is stored correctly and not administered to you after the stated expiry date.

6. FURTHER INFORMATION

What YTRACIS contains

- The active substance is Yttrium (^{90}Y) chloride.
  Each millilitre of solution contains 1.850 GBq of Yttrium (^{90}Y) chloride at the date of calibration.(GBq : GigaBecquerel, Becquerel is the unit in which radioactivity is measured).
- The other ingredients are hydrochloric acid and water for injections.

What YTRACIS looks like and contents of the pack

YTRACIS is a radiopharmaceutical precursor.

This medicine is a clear and colourless solution which is packed in a colourless Type I glass 2-ml vial closed with Teflon-coated bromobutyl rubber stopper and aluminium overseal.

A vial contains 0.5 ml (0.925 GBq at calibration) to 2 ml (3.700 GBq at calibration).

Marketing Authorisation Holder and Manufacturer

CIS bio international
Boîte Postale 32
F-91192 Gif-sur-Yvette Cedex
FRANCE

This leaflet was last revised in ().

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

The following information is intended for medical or healthcare professionals only:
For detailed information refer to the Summary of Product Characteristics of YTRACIS.