# SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of Ytracis. For information on changes after approval please refer to module 8.**

## 1. Introduction

Ytracis is a radiopharmaceutical precursor solution for the in-vitro radiolabelling of specific carriers, such as monoclonal antibodies, peptides or other chemical vectors for radiotherapeutical or diagnostic applications. The nature of the disease to be treated will be determined by the pharmaceutical substance to be radiolabelled. Yttrium-90 chloride is not intended to be administered directly to patients.

The therapeutic use of radioisotopes was recognised in the mid 20th century following the discovery of methods for production of artificial radioactivity. The objective of radionuclide therapy is to achieve appropriate treatment through delivery of a cytotoxic absorbed radiation dose to the desired target and prevent or minimise toxicity to normal tissues. The established use of in-vivo radiotherapy has been restricted to a small number of diseases where isotopes are concentrated selectively in diseased tissues as a result of their normal distribution, e.g. Iodine-131 in the treatment of hyperthyroidism and differentiated thyroid carcinoma, and Strontium-89 for palliation of bone pain from metastatic cancer.

The concept of targeted in-vivo therapy with isotopes conjugated to a carrier molecule, to achieve selective radiation of diseased cells, while sparing healthy cells, has been the subject of research from the 1950's onwards. Initially the majority of attempts to develop targeted radiotherapy e.g. radio immunotherapy, focused on ^{131}I as the radioisotope. [131]I is readily available and inexpensive, its radiochemistry is well known and it can be easily bound to carrier molecules such as antibodies. However, disadvantages of the use of ^{131}I are a possibly unstable linkage to the carrier molecule, quite weak energy of its therapeutic beta rays, and the emission of gamma rays resulting in exposure of the environment to unwanted radiation.

Therefore researchers have looked for a more optimal isotope for systemic radiotherapy and attention has focussed on the high-energy beta emitter Yttrium-90 as a precursor for the labelling of carrier molecules.

## 2. Chemical, pharmaceutical and biological aspects

### Composition

The product consists of an yttrium [$^{90}$Y] chloride solution in 0.04 M HCl with the following composition.

| Ingredients | Quantity | Function |
|---|---|---|
| Yttrium [$^{90}$Y] chloride | 1850 MBq at calibration date | Active ingredient |
| Hydrochloric acid | 4.86 μl | pH agent |
| Water for injections | Up to 1 ml | Solvent |

Packaging materials are common for the type of products (2 ml Ph. Eur. type I colourless glass vial with teflonised rubber stopper and aluminium cap). The secondary packaging consists of a lead pot with sponges, packed in polystyrene blocks in a tin can, packed in an outer carton with wedging. Volumes of 0.5-2.0 ml per vial (925-3700 MBq) will be made available.

### Active substance

[$^{90}$Y] is obtained from [$^{90}$Sr] which in turn is obtained by purification of irradiated uranium-235 according to the following decaying chain.
$$^{235}U + {}^1n \rightarrow \rightarrow \rightarrow {}^{90}Kr \rightarrow {}^{90}Sr \rightarrow {}^{90}Y \rightarrow {}^{90}Zr \text{ (stable)}$$
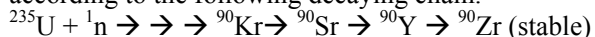
[$^{90}$Sr] is produced by extraction and purification of fission products of uranium after irradiation with thermal neutrons. Fission results in $^{90}$Kr and $^{144}$Ce leading to the progeny of the former, [$^{90}$Sr], which is separated from the isotope mixture by concentrated nitric acid and lead nitrate.

[$^{90}$Sr] Decays by emission of beta radiation with a maximum energy of 0.546 MeV to [$^{90}$Y], with a half-life of 28.15 years, and is present in the form of $Sr(NO_3)_2$ with a relative molecular mass of 211,63.

[$^{90}$Y] is separated from [$^{90}$Sr] using bis(2-ethylhexyl)phosphoric acid (HDEHP) in dodecane, followed by subsequent back extraction with hydrochloric acid. Final purification of the yttrium [$^{90}$Y] chloride bulk solution occurs by passage through an resin.

The identity of [$^{90}$Sr] is determined by recording the beta spectrum and the identity of chloride and yttrium-90 is established in the final active substance yttrium [$^{90}$Y] chloride. The specifications for both liquids are adequate. For the resin adequate requirements are stated for capacity, water content, particle size, heavy metals and arsenic

For dodecane and HDEHP the identities are determined with IR spectroscopy and limits have been adopted for heavy metals and content. In addition, the purity of HDEHP is determined by $^{31}$P NMR spectrometry.

Possible impurities in [$^{90}$Sr] are [$^{89}$Sr], [$^{137}$Cs], [$^{147}$Pm], [$^{90}$Zr] and isotopes of ruthenium and cerium. The alpha, beta and gamma impurities are limited in the specifications.

Regarding the process validation data for the yttrium [$^{90}$Y] chloride bulk solution the following criteria have been identified as essential : strontium content because of its high toxicity and biological kinetic profile, levels of metallic and organic impurities, which can interfere with labelling through complexation by DTPA, and sterility of the resin column.

In-process controls are performed on radioactive concentration, filling volumes, sterilisation and the environment. Specifications for the $^{90}$Sr source are set for appearance, radionuclidic identification, radioactive concentration, radionuclidic purity, gamma-impurities, beta-impurities, alpha-impurities and specific activity.

*Specifications of active substance*

[$^{90}$Y] bulk solution is tested for alpha-, beta-, and gamma- impurities, [$^{90}$Sr] content as well as appearance, identity, metallic impurities, acidity, radiochemical purity and radionuclidic purity.

*Stability of active substance*

The shelf life for strontium [$^{90}$Sr] nitrate which is 4 weeks at 18-25°C in glass vial in lead container is based on stability studies in which three batches were stored during 4 weeks at ambient conditions (18-25°C). Parameters investigated were identity, appearance and radionuclidic purity as well as radioactive concentration at calibration date. Radionuclidic purity remains at ≥ 99.5% and therefore supports the claimed shelf life.

Release requirements for [$^{90}$Y] bulk solution are the same as those for the finished product with the exception of sterility and bacterial endotoxins. Testing is performed for appearance, identification, metallic impurities, acidity, radiochemical purity, and radio nuclidic purity (0.74 MBq $^{90}$Sr/ 37 GBq $^{90}$Y). Storage of maximal 36 h in the manufacturing hot cell is therefore acceptable. A re-test period for the [$^{90}$Y] bulk solution is not relevant as all of the bulk solution is used for the production of the finished product.

## Other ingredients
The specifications of the excipients comply with Ph Eur monographs with additional limits for concentrated HCl. Compliance with requirements are supported by batch analyses results.

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**Product development and finished product**

Ytracis is intended for labelling of various compounds. As further chemical chelation must be achieved, it was logical to chose the liquid form. This radiopharmaceutical is to be processed with either proteins (such as monoclonal antibodies), peptides of any other molecule of biological interest. Thus, yttrium [$^{90}$Y] had to be supplied as a simple salt, in this case the chloride salt.

0.04 M HCl was found to be a good diluent for [$^{90}$Y] chloride for the following reasons
- Chloride is also present in the active substance which prevents subsequent mixture of salts
- At neutral and alkaline pH, the yttrium salt undergoes hydrolysis. The subsequent complex would not react in the same way as a chloride salt. At pH above 4, adsorption on glass becomes a concern. Therefore acid formulation is necessary.
- The acidic formulation furthermore allows the users to easily buffer the solution or to yield their own specific labelling conditions by addition of low concentration of reactants.

The high radioactive concentration of 1850 MBq/ml is adequate for therapeutical use and is consistent with safe as well as easy handling and accurate and sterile withdrawal.

The finished product is prepared by dilution of the yttrium [$^{90}$Y] chloride bulk solution with 0.04 M HCl to obtain an activity of 1850 MBq/ml at calibration date. The solution is filled into 2 ml vials and is sterilised during 20 minutes at 121°C.

The industrial batch size is 30 vials with a fill volume of 0.5 ml up to 2 ml.

The radioactive concentration of the finished product is determined in-process and must be within 1665-2035 MBq/ml (90-110% of declared).

*Specifications of the finished product*
Release requirements for the finished product are the same as those for [$^{90}$Y] bulk solution with the addition of sterility and bacterial endotoxins.

The specification is given below, since the quality aspects must be compared with those required by the marketing authorisation holder of any prospective carrier molecule, e.g. monoclonal antibody, in order to achieve efficient labelling. (Important quality characteristics of a radiolabelling precursor necessary for efficient radiolabelling should be stated in the SPC and package leaflet of the carrier product.)

| TESTS | METHODS | SPECIFICATIONS |
|---|---|---|
| Characters of the solution | Visual inspection | Clear, colourless solution, free of particulate matter |
| Radioactive concentration (at calibration date) | Ionisation chamber | $1665 \leq$ MBq/ml $\leq 2035$ |
| Chloride identification | Precipitation | Complies with the test |
| Acidity | Acidimetric assay | $0.035 \leq M \leq 0.045$ |
| Radionuclidic identification | Liquid scintillation | Complies with the test |
| Radionuclidic purity (at calibration date) : | | |
| $^{90}$Sr content | Liquid scintillation | $\leq 0.74$ MBq $^{90}$Sr / 37 GBq $^{90}$Y |
| γ radionuclidic impurity | γ spectrometry | $\leq 0.001$ % |
| Radiochemical purity of yttrium chloride solution | TLC | $\geq 97.0$ % |
| Metal impurities : | | |
| Cd | | $\leq 1$ µg/ml |
| Cu | | $\leq 1$ µg/ml |
| Fe | Polarography | $\leq 10$ µg/ml |
| Pb | | $\leq 5$ µg/ml |
| Zn | | $\leq 5$ µg/ml |
| Sterility | Direct inoculation | Sterile |
| Bacterial endotoxins | LAL | $\leq 25$ IU/ml |

A labelling procedure for a monoclonal antibody is described. This resulted in a radiochemical

purity of ≥ 95% (six batches of yttrium [$^{90}$Y] chloride were tested). Hence, it is demonstrated that the product at issue is indeed capable of labelling carriers with sufficient efficiency, with acceptable radiochemical purity.

## Stability of the Product

The calibration date is three days after manufacture and the proposed shelf life is four days after calibration date (seven days after manufacture). No special storage conditions are required. Batch testing has been performed at the dates of manufacture, calibration and expiry. All release parameters were investigated, though radionuclidic identity and purity were only investigated at release. In addition to the release parameters the radiochemical purity of a radiolabelled antibody preparation has been investigated.

Results comply with the end of shelf-life specification and the proposed shelf life of four days after calibration is acceptable.

## Discussion on chemical, pharmaceutical and biological aspects

This is an unusual medicinal product, as it has no specific indication alone and must not be injected directly to the patient. It is a 'precursor' to be used solely for *in vitro* radiolabelling of carrier molecules which themselves will ultimately decide the target and clinical indication for the radiolabelled molecule. However, this product must (and does) comply with the usual quality requirements relating to parenterals as defined in the Ph Eur. In addition, it is important to define the quality characteristics, which will ensure efficient radiolabelling, and these have been defined and controlled in this case (e.g. radiochemical purity, radionuclidic purity, freedom from trace metal contaminants which may interfere with labelling, etc.).

Considering the short half-life of $^{90}$Y and the resulting time constraints during manufacture, some important tests are performed 'retrospectively', e.g. radionuclide purity, sterility and pyrogens, although this is unavoidable in this case and is normal for such products in general. Again, considering the time constraints and short half-life, stability issues are perhaps not as important as for other products intended to be stored for long periods of time.

The chemical-pharmaceutical information is well documented and describes adequately the quality of the active substance and the finished product and the manufacturing of the finished product.

## 3. Toxico-pharmacological aspects

Yttrium [$^{90}$Y] chloride [YCl$_3$] sterile solution CIS bio international is a precursor solution for the *in vitro* radiolabelling of other radiopharmaceuticals, which may be indicated for targeted radiotherapy. As precursor, Yttrium [$^{90}$Y] chloride sterile solution has no intended clinical usage as such. Yttrium [$^{90}$Y] is a sterile solution, which contains a maximum of 3.7 GBq (100 mCi) of Yttrium chloride [$^{90}$YCl$_3$] at a reference time.

In addition to the standard requirements laid down in the EU legislation which apply to all the medicinal products, some specific provisions for radiopharmaceuticals are set out in Council Directive 89/343/EEC of 3 May 1989. Moreover, the assessment of application dossiers for radiopharmaceuticals must take into account the specific information relevant to these products. Concerning the toxicological and pharmacological tests (as defined in part 3 of the annex to the Council Directive 75/318/EEC of 20 May 1975):

-    GLP compliant studies would be preferred, however, bibliographic evidence may be accepted provided that studies were conducted to GLP-like quality standards or that any issues arising from regulatory review can be adequately dealt with by reference to the original bibliographic information provided.

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- Questions related to poor labelling efficiency and *in vivo* dissociation of the radiolabelled immunoconjugate must be addressed. The effects that may be produced by the potential circulation of free Yttrium [$^{90}$Y] chloride in the body must be addressed. Information relating to single and repeated dose toxicity must be provided. Information on chemical toxicity and disposition of the 'cold' (i.e. non-radioactive) product may be relevant.
- Mutagenicity studies (performed with the radioisotope) on are considered not to be useful since the results will confirm effects that are known and expected.

### Internal radiation dosimetry

Dosimetry of the labelled radiopharmaceutical will depend on the pharmacokinetics of the carrier to be labelled. The applicant has submitted an evaluation of the internal radiation resulting from the free $^{90}$Yttrium ($^{90}$Y$^{3+}$) that could be administered unconjugated or released from the protein conjugates.

No definitive conclusion can be drawn regarding the safety of high and low Yttrium doses toward the offspring. For both embryo-foetal and perinatal toxicity, if Yttrium follows the pattern of the other rare earth elements, a risk is probably implied but the very low doses of Yttrium administered in radioimmunotherapeutic applications should balance the effective concerns.

The calculation was effected in agreement with MIRD/ICRP 60 recommendations.

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

| Organ | Adult male 70 kg | Adult female 57 kg | 15 years | 10 years | 5 years | 1 year | New Born |
|---|---|---|---|---|---|---|---|
| Absorbed dose per unit activity administered (mGy/MBq) |
| 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 1GBq is 700 mSv for a 57 Kg female adult and 650 mSv for a 70 Kg male adult.

### Pharmacodynamics

Yttrium [$^{90}$Y] chloride [$^{90}$YCl$_3$] is not intended to be directly administered to the patient and no pharmacodynamic effect is sought neither for the radionuclide (unconjugated) nor for the (cold) Yttrium chloride itself. Some bibliographic data concerning the pharmacodynamic effect of cold Yttrium [$^{89}$Y] are available. From these data no primary or secondary pharmacodynamic effects of Yttrium chloride are expected from the use of Yttrium chloride.

- *In vitro* studies

No original *in vitro* studies have been performed.

- *In vivo* studies

A few pharmacodynamic studies deal with doses of Yttrium chloride several orders of magnitude larger than the maximal dose (20 to 200 ng) which could theoretically be administered to the patients. They demonstrate that any pharmacodynamic effect can be excluded from the release of (cold) Yttrium chloride at therapeutic dosages of conjugates.

*Histological studies*

When administered to rats, Yttrium chloride accumulates in the liver in the spleen and in the bones. At 50 mg/kg administered intravenously, but not at 10 mg/kg, it induces a spleen granuloma in rats, but not in the liver (Nakamura *et al*. 1991). A study (Hirano *et al*. 1993) confirmed these findings; the intravenous injection of cold Yttrium chloride ($YCl_3$) at doses higher than 200 µg/rat induced the formation of a colloidal material composed of proteins and some minerals. Phagocytic cells in the liver and in the spleen take up this colloid. Yttrium chloride is deposited in lysosomal inclusions of Kupffer cells and macrophages; the half time of the hepatic clearance is approximately equals to 144 days. At a dose of 1 mg /rat, a large amount of calcium is deposited in the liver (representing more than 10 times the amount of calcium normally present in this organ) and spleen (over 100 times) and a slight increase is observed in the lung and kidney (less than 1.5 times).

*Biochemical studies*

Yttrium chloride administered intravenously increased the calcium concentration of liver, spleen and lung in rats; the distribution of calcium matched the distribution of Yttrium chloride in liver, but not in lung and spleen (Nakamura *et al*. 1993; Hirano *et al*. 1996). In the same studies Yttrium chloride ($YCl_3$) transitorily increased blood calcium concentration probably through bone resorption (Hirano *et al*. 1996). No apparent changes were observed in magnesium and phosphorus (Nakamura *et al*. 1993). In a study (Nakamura *et al*. 1993) a slight effect of Yttrium ($Y^{3+}$) on serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) following the administration of 10 mg/kg Yttrium chloride intravenously to rats 24 and 72 h after the injection was observed. In a second study (Hirano *et al*. 1996) both aminotransferases were dramatically increased following the administration of 1 mg of Yttrium chloride per rat intravenously. These effects may be explained by the colloidal form of Yttrium chloride in the blood that triggers the activity of phagocyte cells in the liver and spleen.

The significance of the observed effects has apparently not been fully interpreted by the authors of the studies. The calcium mobilisation occurs rapidly after Yttrium chloride administration. The Yttrium chloride under its colloidal form accumulates preferentially in phagocytic cells in the liver and spleen. The transitory increase of aspartate aminotransferase and alanine aminotransferase and the accumulation of calcium in the liver and spleen may indicate that these organs are primary targets for high doses of Yttrium chloride administered intravenously (corresponding approximately to $10^5$ times the dose administered during a radioimmunotherapy treatment). It is unknown whether or not Yttrium ($Y^{3+}$) is in a colloidal form when used at low concentrations (e.g. radioimmunotherapy).

- Pharmacodynamic drug interactions

No information regarding interaction of Yttrium chloride with other medicinal products was available. Free Yttrium ($Y^{3+}$) could complex chelating agents such as EDTA (ethylene diamine tetraacetic acid) which may modify its *in vivo* behaviour, leading to rapid renal elimination.

- General and safety pharmacology programme

For the reasons mentioned above no original general and safety pharmacology programme was performed.

**Pharmacokinetics**

The pharmacokinetics properties (i.e. the distribution) of Yttrium depend on the dose of product administered (Nakamura *et al.* 1991). Several pharmacokinetic studies using high doses of (cold) [89]Yttrium chloride or low doses of either radioactive [90Y] or non-radioactive [89]Yttrium have been published. The studies performed with low doses of radioactive Yttrium chloride are the most relevant to characterise the disposition of the Yttrium [90Y] released after an *in vivo* dissociation of the radiolabelled immunoconjugate.

The pharmaco-toxicological interpretation of pharmacokinetic data is made difficult by the influence of injected compounds particle sizes and chemical form (chelated or unchelated) on the biodistribution.

Depending on Yttrium [90Y] chloride serum concentration colloids of varying particle sizes are formed, which may explain marked differences in term of biodistribution. Ramsden *et al.* 1961 described that solutions of colloidal Yttrium chloride over a range of particle sizes prepared by varying the citrate/Yttrium chloride ratio had different biodistributions after intravenous injection in rabbits. The large particles cleared rapidly and distribute mainly to the liver and to the spleen. The smaller particles clear slowly and distribute to the bone and to the bone marrow. The particles of intermediate size concentrate approximately after 18 hours equally in bone and liver. The concentration increases with the time in bone and decreases in other organs. Some Yttrium chloride remains at the site of injection (The exact particle sizes are not stated). These observations are difficult to extrapolate to the extremely low dosages used in radionuclide therapy. At the concentrations used for radiolabelling purposes, the amount of radiocolloid formed as complex salts through interaction with plasma or blood proteins is likely to be extremely low.

- Pharmacokinetics after a single dose

- *Pharmacokinetics properties of Yttrium administered at <u>high doses</u>*

A study (Nakamura *et al.* 1991) explored the pharmacokinetic properties of Yttrium chloride at high doses (10 and 50 mg/kg) administered intravenously to rats. Similar doses of some rare earth elements Europium (EuCl$_3$), Dysprosium (DyCl$_3$) and Ytterbium (YbCl$_3$) were also given intravenously and the pharmacokinetic properties of these elements were compared to those of Yttrium chloride.

At these concentrations Yttrium chloride accumulates mainly in the liver, the spleen and in the bone. The excretion of Yttrium chloride and the rare earth elements occurs gradually in the faeces over a period of 7 days. No Yttrium chloride or rare earth elements are detected in the urine. A small quantity of Yttrium chloride is found in the kidney, in the pancreas and in the heart.

Yttrium chloride disappeared from whole blood within 4 hours. The distribution in the liver was the highest between 8 hours and 2 days after the administration. The fraction of the dose of Yttrium chloride found in the spleen was higher than for the other rare earth elements and increased over the time of the experiment. The distribution of Yttrium chloride in the bone increased gradually as well over the time of the experiment.

Nakamura *et al.* 1993 determined that following an intravenous administration of 10 mg/Kg of Yttrium to rats the half-life of Yttrium in the whole blood was 0.427 hours and 19.3 days in the liver (the concentration of Yttrium in the whole blood and the liver decreased exponentially over the time period between 8 hours to 4 days following administration of Yttrium chloride).

The tissue distribution and the subcellular localisation of Yttrium chloride were studied in rats (Hirano *et al.* 1993). Yttrium chloride was been administered at different dosages ranging from 0.1 to 2 mg/rat. The animals were sacrificed 1 hour after the injection. The control groups received 0.2 ml saline intravenously. The animals were sacrificed 1h, 14, 28, 91 and 182 days after the injection. At 1 mg/rat, the blood Yttrium chloride content decreased rapidly within 3 hours; about 75 % of the dose

was accumulated in the liver and 20 % of the dose in the spleen at 7 hours post injection. The concentrations of Yttrium chloride in the liver decreased slowly with a halftime of 144 days. At the concentration tested most of Yttrium in blood plasma was found in the colloids which are rapidly cleared and distributed as such in tissues.

All three studies show that, at high dose, Yttrium injected by intravenous route accumulates primary in the liver and spleen. After an intravenous injection Yttrium chloride at high doses leads to formation of a dose dependent colloidal material in the blood, composed of proteins and other minerals (Calcium, Strontium, Sulfur, Iron, Phosphorus). Kupffer cells and macrophages in the spleen subsequently take up this colloidal material.

Different elimination half-lives (from the liver) has been published by Nakamura *et al.* 1993 and Hirano *et al.* 1993. They are equal respectively to 192 and 144 days. This might be explained by differences between injected doses (10 mg and 1 mg) leading to the formation of dose-dependent colloid materials, with different particle sizes and then different elimination patterns. Taking these elements into consideration, it can be assumed that after the administration of $^{90}$Yttrium (even at low doses) the decay into zirconium occurs before the first elimination half-life in the liver elapses [the emission half-life of $^{90}$Yttrium is equal to 64 hours].

In conclusion, Yttrium [$^{90}$Y] chloride injected intravenously is present in plasma as a colloid and is then taken up by the liver, spleen and bone within a few hours. Yttrium chloride is found in the liver and spleen in higher quantities than in other organs. Considering increased activity of the phagocyte cells in these organs respectively 75% and 20% of free Yttrium chloride accumulated there, seven hours after the administration. In the prospect of the use of $^{90}$Yttrium as a conjugate for radioimmunotherapy the quantity and activity of Yttrium [$^{90}$Y] chloride, which will distribute in the body will be determined by its conjugation with the ligand and the therapeutic indication(s).

- *Pharmacokinetics properties of Yttrium administered at <u>low doses</u>*

In a study performed by Durbin *et al.* 1960 a small amount of $^{91}$Yttrium chloride (the exact dose is not stated in the publication) was administered intramuscularly to rats [Note: $^{91}$Yttrium is a beta emitting isotope of Yttrium with half-life equal to 58.51 days]. Four days after the administration $^{91}$Yttrium chloride distributed mainly in the bones (55.6 % of the initial dose) and in the liver (12.1 % of the initial dose).

The study of the distribution of $^{88}$Yttrium (0.5 mCi/mouse) administrated intravenously in mice (Gansow 1991) showed that at 24, 48 and 168 hours this isotope of Yttrium mainly accumulates in vertebrae, pelvis, femur, kidney and liver. The amount of $^{91}$Yttrium in bones is stable between 24 and 168 hours and is approximately equal to 20% of the injected dose per gram of bone in mice. Further kinetic studies indicated that $^{90}$Yttrium is quickly located in the femurs (80% of the dose administered); the elimination half-time was 62 hours (this is close to the emission half-life of the isotope $^{90}$Yttrium which is equal to 64 hours). The uptake of Yttrium in the femoral marrow and muscle is small. Only 2 % and 1 % of the activity of the femoral bone are found in the femoral marrow and in the muscle respectively.

In rabbits and dogs, Yttrium concentrated on bone surfaces (Jowsey *et al.* 1955). Yttrium was not found in either osteoid tissue or in areas of active calcification. In another study twenty-four hours after an intraperitoneal injection of 500 pCi/kg of $^{91}$Yttrium chloride to puppies, (Jowsey *et al.* 1958) $^{91}$Yttrium chloride accumulated on bone surfaces, which are mineralised, and mostly in the epiphyseal bone. Yttrium was taken up in the skeleton and appeared on non-growing highly calcified bone surfaces. Yttrium was taken up by bone mineral and localised on the available resorbing and inactive surfaces of bone tissue.

The literature results consistently show that Yttrium is intensively fixed on bones when administered at low doses, the bone uptake of radioactive Yttrium [as $^{90}$Yttrium chloride] may secondarily induce a myelosuppression.

Watanabe *et al.* 1999 investigated the use of disodium calcium edetate (CaNa$_2$EDTA) in case of [90]Yttrium poisoning [note: disodium calcium edetate is a salt of EDTA and a chelating agent used in therapeutics] to prevent or treat any radiomyelosuppression. In this study disodium calcium edetate was not able to complex [90]Yttrium once fixed on the bones but chelated [90]Yttrium before its deposition.

- *Conclusions on Pharmacokinetics after the administration of a single dose of Yttrium*

In conclusion, administered by intramuscular, intraperitoneal or intravenous injection at low dose in carrier-free form to experimental animals radioactive Yttrium [^{90}Y] chloride accumulates mainly in the bones and is retained. At low concentrations Yttrium [^{90}Y] chloride seems to be mainly adsorbed on the mineral parts of bones and/or is bound by strong electrostatic forces to carbamyl and sulfate groups of the bone tissue. However, mechanisms of retention are still unclear. There are conflicting opinions about the formation of colloid at these low concentrations.

The uptake of [90]Yttrium in the muscle and femoral marrow is small, achieving maximum activities per gram that is only about 1 % and 2% of the activity per gram in the femoral bone, respectively. There are no data in the literature about Yttrium elimination in faeces or urine at these concentrations, with the exception of a study (Jowsey *et al.* 1956). This study describes a total urine and faeces (combined) elimination of 8 to 10 % of the injected dose (rabbits, dogs, 500 à 1000 µCi/kg of [91]Yttrium).

Pre-injection of chelators increase the elimination rate of [90]Yttrium in the urine. Since Yttrium is intensively fixed on bones when administered at low doses, the bone uptake of radioactive Yttrium [as [90]Yttrium chloride] may secondarily induce a myelosuppression.

• Pharmacokinetics at repeated doses

A repeated dose study confirmed the pharmacokinetic properties of Yttrium. Yttrium chloride was given to rats in the peritoneum at 60 mg/kg every two days for 5 months. The level of Yttrium in the femur was at the maximum equal to 100 times the uptake of strontium given at a similar dose. In case of repeated doses, one issue is the fate of [90]Zirconium produced by the decay of [90]Yttrium (maximum 1 µg). Zirconium is found in the alimentation (notably vegetables). A standard diet is estimated to provide 3.5 mg of zirconium daily. Zirconium can be detected in several organs such as the brain, the kidney, the liver, the lungs, muscles, in fat tissues and in lymph nodes. Zirconium is concentrated in erythrocytes. In the whole blood zirconium levels are between 0.012 and 1.25 µg/g (Berman 1980). These endogenous levels of Zirconium are extremely high in comparison with the possible concentrations resulting from the decay of 90Yttrium chloride. Overall the repeated administration of Yttrium chloride could possibly induce an accumulation of Yttrium in the bone marrow. The literature data suggest that repeated administrations lead to accumulation of Yttrium in the bone but this accumulation is subject to a limitation.

The quantities of Yttrium [^{90}Y] chloride administered during a treatment by radioimmunotherapy are such that any interference of previous injections are unlikely, except for the radiobiological effects at the bone marrow levels which may be cumulative. However, this risk may be balanced by the fact that in a standard radioimmunotherapy the subsequent doses of [90]Yttrium are generally given after the complete decay of the previous injection of [90]Yttrium.

## Toxicology

No original single dose or repeated dose toxicity studies were submitted. The published single dose and repeated dose toxicity studies have been performed with cold (i.e. non radioactive) Yttrium.

• Dose extrapolation

It is expected that a patient will be exposed to an activity of 1.850 GBq (50 mCi), which corresponds approximately to 1.8 ng/kg for a person of 50 kg. According to product specification, 1 ml of [90]Yttrium chloride solution contains 1.850 GBq (50 mCi) of [90]Yttrium chloride.

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Radioactive Yttrium is usually linked to a carrier. Assuming a standard situation with a radioincorporation rate for [90]Yttrium of 90%, therefore 0.18 ng/kg of free [90]Yttrium might be present in the formulation. This is substantially lower than the toxic dose levels reported in the literature (10 and 50 mg/kg of Yttrium chloride in rats).

- Single dose toxicity

Hirano *et al.* 1993 conducted single dose intravenous toxicity studies in rats. One milligram of Yttrium and 0.1, 0.2, 0.5 or 2 mg of Yttrium have been administered to rats. Following administration, Yttrium was predominantly distributed to plasma in the blood. At doses superior to 0.2-mg Yttrium/rat, most plasma Yttrium appeared to be in the colloidal material, which was composed of proteins and some minerals. Electron microscopic analyses revealed that phagocytes in the liver and spleen took up the colloidal material. The liver Yttrium was slowly cleared with a half-life of 144 days at a dose of 1-mg yttrium/rat (see Pharmacokinetics above). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities in plasma were increased with a peak 20 hour after the administration of 1 mg Yttrium/rat and returned to their control values at 170 hour after the administration. Nakamura *et al.* 1993 found a slight effect of the administration of Yttrium on glutamic-oxaloacetic and glutamic-pyruvate-transaminase serum activities 24 and 72 hours following the administration to rats of 10-mg Yttrium/kg intravenously. This confirms previous findings of Hirano *et al.* 1993. Hirano *et al.* 1993 reports that at a dose of 1 mg Yttrium/rat, a significant and tremendous amount of Calcium was deposited in the liver (over 10-fold) and spleen (over 100-fold). Yttrium chloride given intravenous to rats increased calcium concentration in liver, spleen and lung. Yttrium chloride transitorily increased blood calcium concentration but no obvious changes were observed in magnesium and phosphorus (Nakamura *et al*. 1993, Nakamura *et al*. 1996, and Hirano *et al*. 1993).

The lethal doses 50 (LD50) values published for Yttrium in the literature were in the range of 45 to 515 mg/kg, depending on the administration mode, animal model and chemical form of the metal. Further studies performed with Yttrium nitrate found that the lethal doses 50 (LD50) were 350 mg/kg (in frogs after a subcutaneous administration), 1660 mg/kg (in mice following a subcutaneous administration), 20 - 30 mg/kg (in rat after an intravenous administration) and 500 mg/kg (in rabbits after an intravenous administration, Haley 1965).

In rats and mice, after receiving 12.5, 25, 37.5, 50, 75, 150 and 300 mg/kg Yttrium, Kyker *et al*. 1957 found a LD50 for Yttrium of $45 \pm 2.1$ mg/kg (in rats) and $88 \pm 11.7$ mg/kg (in mice), this observation was made 10 days after the administration of the product. The LD50 for Yttrium after an intravenous administration to rabbits was 515 mg/kg.

The published LD50 for Zirconium ranges from 63 to 4100 mg/kg. Other animal studies also indicate a low order of toxicity, whether administered orally or injected (Berman, 1980).

Cochran *et al*. 1950 found that the lethal dose 50 (LD50) for Yttrium and Zirconium after intraperitoneal administration to rats ranged from 117 to 395 mg/kg and 63 to 393 mg/kg, respectively. Orally administered Zirconium showed LD50 ranged from 853-2290 mg/kg.

- Repeated dose toxicity

The applicant has submitted only bibliographic data.

Yttrium chloride was administered at the dosage of 60 mg/kg every 2 days up to 5 months via the intraperitoneal route to rats. In this study the animals did not experience any sign of systemic toxicity. A further study in rabbits shows that intraperitoneal administration of Yttrium chloride for more than 5 months produced only intestinal adhesions and no effect on growth (Haley, 1965). Intratracheal administration of Yttrium, Neodymium and Ytterbium oxides to rats resulted in the production of granulomas after 8 months (Haley, 1965).

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One article from 1980 (Berman, 1980) published a review on the toxicity of Zirconium. Zirconium sulphate was administered to mice (5 ppm in water) appeared to have little effect upon growth and did not prove to be carcinogenic. Its incorporation in deodorants preparations and in lotions has been documented to induce allergic reactions that can lead to axillary granuloma and hypersensitivity reactions. Exposure of rabbits to zirconium lactate mists induced pulmonary granulomata. Zirconium salts can act *in vitro* as lymphocyte mitogens and augment the functional responsiveness of immune cells, which may explain the delayed hypersensitivity and immunological granulomas (Price and Skilleter, 1986).

Since $^{90}$Yttrium will be given at very low concentrations the absence of original repeated toxicity studies may be justified. However, the toxic effects of high dose of free Yttrium, the effect of its colloidal form on the accumulation in the liver and spleen, and the toxicity of the high doses of stable Zirconium should be considered. When high doses of Yttrium have been administered to rats granuloma formation in the spleen has been observed (Nakamura *et al.* 1991).

Zirconium [resulting from the decay of $^{90}$Yttrium] could lead to the immunology response of the phagocytic cells in the liver and spleen. In an *in vitro* study using lymphocytes, Zirconium salts were found to be mitogenic. The liver, spleen and bone can be considered as primary target organs for Yttrium chloride. The presence of phagocyte cells in the liver and the spleen suggest that an aspecific immunological reaction occurs after an administration of Yttrium. This may be due to the presence of the colloidal form of Yttrium chloride in the blood.

Finally, since a potent chelating agent is present in the preparation to be administered to patients, only a very little amount of Yttrium should be present in the organs. At the dose recommended for human no systemic toxicity linked to the Yttrium (as a non radioactive product) is expected. However, in the event that free radioactive $^{90}$Yttrium is released the expected toxicity should be linked to its radiobiological effects.

- Genotoxicity

No specific studies have been performed to evaluate the mutagenic potential of Yttrium.

Although the mutagenicity of the metal is still unknown, the mutagenic potential of $^{90}Y^{3+}$ relates to the effects of radiations. From the biodistribution studies, it seems that the spleen, the liver and especially the bone marrow are the target organs for unconjugated $^{90}Y^{3+}$. Some studies performed with $^{90}Y$ citrate administered intravenously in mice induced DNA damage in bone marrow erythroblastoid cells that could be measured by subsequent scoring of micronuclei in peripheral blood reticulocytes. A treatment of mice with 370 and 1,110 kBq (these doses are close to the doses administered in humans) induced the formation of 1.33 % and 2.28 % of micronuclei in peripheral blood reticulocytes (MnRETs) 2 to 4 days after administration (Lenarczyk *et al.* 2001). $^{90}$Yttrium also induced micronuclei in human peripheral blood lymphocytes (Mill *et al.* 1996). In mice, the survival of bone marrow granulocyte-macrophage colony-forming cells (GM-CFC) was reduced by intravenous administration of $^{90}$Yttrium citrate (Goddu *et al.* 1998).

- Carcinogenicity

In accordance with the current requirements for radiopharmaceuticals, no carcinogenicity studies were performed with $^{90}$Yttrium chloride.

- Reproduction toxicity

- *Fertility and early embryonic development*

No data are available on the chemical toxicity of yttrium toward the reproductive function. The radiotoxicity is the most relevant risk with regard to the reproductive function.

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The biodistribution study performed by the applicant indicates that the uptake of Yttrium in the testes is very low.

A low fraction of orally administered Zirconium (dose, 0.23 g/kg/day in mice) is selectively fixed in the ovaries, inducing hypervascularisation one month after the end of treatment (Delongeas *et al.* 1983). This observation is not relevant to the Zirconium resulting from the decay of Yttrium, which is expected to be located mainly in bones.

The lack of further studies is reflected in the proposed Summary of Product Characteristics for Yttrium.

- *Embryo-foetal development*

A few studies on animals demonstrated the transfer of certain radioactive rare earth elements (REEs) from mother to offspring via the placenta.

- *Perinatal development*

A few studies on animals demonstrated the transfer of certain radioactive rare earth elements (REEs) from mother to offspring via the milk.

- Local tolerance

The applicant has not provided any information on local tolerance.

- Ecotoxicity/Environmental risk assessment

The applicant has submitted an assessment of environmental risks. The use of $^{90}$Yttrium chloride is not considered to be associated with unacceptable environmental risks provided that the regulations concerning the handling and disposal of radiopharmaceuticals are adhered to (see paragraph below).

- *Occupational Hazards*

Radiopharmaceuticals 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. The user should prepare radiopharmaceuticals in a manner, which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, and sterility should be maintained throughout the labelling procedures. The application has proposed information in the summary of product characteristics section 4.4 Special warnings and special precautions for use.

**Discussion on toxico-pharmacological aspects**
$^{90}$Yttrium is a precursor (to be used for radiolabelling purposes) for combination with other medicinal products consisting of a suitable linker (chelator) and a disease-specific carrier. The $^{90}$Yttrium precursor is not to be given directly to patients.

No information was provided as GLP compliant studies.

Due to the low systemic exposure of $^{90}$Yttrium chloride primary or secondary pharmacodynamic effects are not considered likely or relevant for the application. Appropriate information on the therapeutic use should be included in the dossier of any carrier/linker using $^{90}$Yttrium as radiolabel.

In animals, Yttrium administered intravenously was present in plasma as colloid and it was taken up in few hours by bone with a greater binding than calcium. It can be found in relatively moderate quantities also in liver and spleen. There was almost no biological clearance from bones.

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Dosimetry data on $^{90}$Yttrium have been provided in the application in order to evaluate the contribution of non-conjugated 'free' $^{90}$Yttrium to the radiation dose following the administration of $^{90}$Yttrium-labelled medicinal products, or following accidental administration of the precursor. These calculations were done according to the MIRD/ICRP 60 recommendations based on studies using male rats. As no real alternative is presently available for the estimation of radiation dose, the use of the MIRD approach remains acceptable. The biodistribution studies are in accordance with the literature data, and they show a relatively high and stable uptake by the bones with high-absorbed doses to the red marrow and the bone surface. Because of high Weighting Factor - indicating high radiosensitivity - relatively high values of the Effective Dose highlights the importance to prevent presence of 'free' $^{90}$Yttrium in conjunction with therapeutic administration of the labelled medicinal product.

Single dose intravenous distribution and toxicology studies indicate that Yttrium will be rapidly cleared from plasma and it will mainly locate in bone mineral. High dose target organ toxicity might include the liver and the spleen.

No supplementary animal studies are needed because 1) relevant safety issues can adequately be evaluated from the literature, 2) animal welfare reasons, and 3) the fact that single and repeated dose toxicity studies will be provided for the carrier medicinal products using the $^{90}$Yttrium radiolabel.

Mutagenicity and carcinogenicity studies are not relevant for this product.

An environmental risk assessment report has been submitted. Potential environmental risks are acceptable. The information on occupational hazards will be included in section 4.4 Special warnings and special precautions for use in the summary of product characteristics, which appears to be appropriate for a radiopharmaceutical precursor.

Non-clinical data show that unconjugated $^{90}$Yttrium accumulates in bones and radiation-induced myelo-suppression is likely to be the most important toxicity (and dose limiting factor) to be observed in the clinical situation.


## 4. Clinical aspects

Nuclear medicine therapy (radionuclide therapy) uses radioactive sources for the selective delivery of radiation to target organs or tumours. The therapeutic use of radioisotopes has been developed in the mid 20th century following the discovery of methods of production of artificial radionuclides. In that respect 131Iodine has been used for the treatment of differentiated papillary or follicular thyroid carcinoma and 32Phosphorus-orthophosphate has been used for the treatment of polycythaemia vera. Potential new applications of radionuclide therapy (particularly in the field of oncology) reflect advances in antibody engineering (radioimmunotherapy), the identification of tumour antigen targets or the synthesis of peptide analogues (peptide therapy). These compounds are subsequently complexed with β– (or α–) emitting radionuclides in order to achieve an appropriate treatment through the delivery of a cytotoxic absorbed radiation dose to the desired target and prevent or minimise the toxicity for normal tissues.

Yttrium [$^{90}$Y] chloride is a β–emitting radionuclide radiopharmaceutical. It is a precursor intended to be used for in vitro labelling of appropriate carriers for subsequent radionuclide therapy.

Concerning the clinical documentation (as defined in part 4 of the annex to the Council Directive 75/318/EEC of 20 May 1975): In the specific case and only in that case of precursors for radiolabelling purposes (such as Yttrium [$^{90}$Y] chloride) the clinical documentation is considered not to be relevant since the precursor itself is not administered as such to the patients.

-   The precursor itself is not the medicinal product, which is administered to the patient, and there is no clinical indication for the precursor per se which needs to be justified with clinical information.

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- Other parallel exists, e.g. new excipients, where the competent authority would expect to see toxicology data but not necessary clinical trials focussed specifically on the clinical performance of the new excipient alone.
- There may be ethical reasons why clinical studies on the precursor alone should not be performed or required.
- In any case, relevant part III & part IV information relating to the clinical use of the labelled product will be available in the dossier of the carrier.

Since Yttrium (Y-90) Chloride Sterile Solution CIS bio international will be exclusively used for the *in vitro* radiolabelling of pharmaceutical substances, such as monoclonal antibodies, peptides or other substrates with the view to radiotherapeutical applications, **Yttrium [$^{90}$Y] chloride should not be administered directly to patients**.

## Clinical pharmacology

No original clinical pharmacology studies were submitted in the application.

- Pharmacokinetics

The biodistribution of $^{90}$Yttrium will be specific to the carrier to be radiolabelled. *In vivo* presence of unconjugated $^{90}$Yttrium may be observed in vivo due to poor chelation, product gradient or protein or peptide digestion releasing unconjugated $^{90}$Yttrium.

## Clinical efficacy

No original clinical efficacy studies were submitted in the application. In fact, information relating to clinical efficacy obtained from the precursor *alone* is considered not to be relevant, in this specific case.

However, sufficient information to support an indication as a radiolabelling agent has been included in this dossier, and this will be further supplemented by the results of relevant clinical efficacy and safety trials in the dossier of any carrier/linker molecule which proposes to use $^{90}$Yttrium as a radiolabel.

The indication proposed is in line with the conclusions of a CPMP *ad hoc* group of experts meeting on radiopharmaceutical precursors, held in April 2001.

## Clinical safety

No original clinical safety studies were submitted in the application.

The safety of this product as a radiolabelling agent will be further supplemented by the results of relevant clinical efficacy and safety trials in the dossier of any carrier/linker molecule which proposes to use $^{90}$Yttrium as a radiolabel.

*In vivo* presence of unconjugated $^{90}$Yttrium may be observed due to poor chelation, product gradient or protein or peptide digestion releasing unconjugated $^{90}$Yttrium. Unconjugated $^{90}$Yttrium accumulates in bones and radiation-induced myelo-suppression is likely to be the most important toxicity (and dose limiting factor) to be observed in the clinical situation.

As for all the radioactive products, 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.

- Safety in special populations

Usual radiochemical precautions should be exercised with regards to use of $^{90}$Yttrium chloride in women of childbearing potential, pregnancy, and in children. Women of childbearing potential should use effective contraceptive means during treatment with an $^{90}$Yttrium chloride medicinal product and for at least 2 months afterwards (20 times the half-life of Y-90). The same applies for lactating

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mothers, as excretion of the product in breast milk cannot be excluded. During treatment and at least for 2 month after termination of treatment, women should be advised to discontinue nursing. Even though distribution of $^{90}$Yttrium chloride to testes is low (in rats), radiation-induced sperm damage cannot be fully excluded, and male patients should be recommended to use contraceptive measures during treatment and for 12 months following treatment (20 times the half-life of $^{90}$Yttrium chloride plus 3 spermatogenesis cycles, 3x100 days). These later recommendations would appear appropriate to include in the summary of product characteristics of the carrier medicinal product.

The summary of product characteristics for Yttrium indicates that the use of $^{90}$Yttrium is contraindicated in case of established or suspected pregnancy or when pregnancy has not been excluded.

- Overdose

Appropriate information has been included in the summary of product characteristics for Yttrium [$^{90}$Y] chloride CIS bio international and should be included in the summary of product characteristics of the carrier medicinal product on the drug-drug interaction potential regarding chelating agents. Chelators like Ca-DTPA or Ca-EDTA must be available in medical institutions which use $^{90}$Yttrium for radiolabelling of carrier molecules. These chelators may be used immediately (i.e. within 1 hour) as an antidote in case that the $^{90}$Yttrium chloride precursor is erroneously given to patients.


## 5. Overall conclusions, benefit/risk assessment and recommendation

### Quality

The important quality characteristics of Yttrium ($^{90}$Y) chloride are well defined and controlled, and the product is formulated, manufactured and controlled in a way that is characteristic of a solution for injection. The specifications and batch analytical results indicate a consistent product that should result in uniform radiolabelling performance from batch to batch. There are no outstanding quality issues which have a negative impact on the benefit/risk balance.

### Preclinical pharmacology and toxicology

Due to the low systemic exposure of $^{90}$Yttrium chloride primary or secondary pharmacodynamic effects are not considered likely or relevant for the application. Appropriate information on the therapeutic use should be included in the dossier of any carrier/linker using $^{90}$Yttrium as radiolabel.

In animals, Yttrium administered intravenously was present in plasma as colloid and it was taken up in few hours by bone with a greater binding than calcium. It can be found in relatively moderate quantities also in liver and spleen. There was almost no biological clearance from bones.

Dosimetry data on $^{90}$Yttrium have been provided in the application in order to evaluate the contribution of non-conjugated 'free' $^{90}$Yttrium to the radiation dose following the administration of $^{90}$Yttrium-labelled medicinal products, or following accidental administration of the precursor. These calculations were done according to the MIRD/ICRP 60 recommendations based on studies using male rats. As no real alternative is presently available for the estimation of radiation dose, the use of the MIRD approach remains acceptable. The biodistribution studies are in accordance with the literature data, and they show a relatively high and stable uptake by the bones with high-absorbed doses to the red marrow and the bone surface. Because of high Weighting Factor - indicating high radiosensitivity - relatively high values of the Effective Dose highlights the importance to prevent presence of 'free' $^{90}$Yttrium in conjunction with therapeutic administration of the labelled medicinal product.

Single dose intravenous distribution and toxicology studies indicate that Yttrium will be rapidly cleared from plasma and it will mainly locate in bone mineral. High dose target organ toxicity might include the liver and the spleen.

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No supplementary animal studies are needed because 1) relevant safety issues can adequately be evaluated from the literature, 2) animal welfare reasons, and 3) the fact that single and repeated dose toxicity studies will be provided for the carrier medicinal products using the $^{90}$Yttrium radiolabel.

Mutagenicity and carcinogencity studies are not relevant for this product.

An environmental risk assessment report has been submitted. Potential environmental risks are acceptable. The information on occupational hazards will be included in section 4.4 Special warnings and special precautions for use in the summary of product characteristics, which appears to be appropriate for a radiopharmaceutical precursor.

Non-clinical data show that unconjugated $^{90}$Yttrium accumulates in bones and radiation-induced myelo-suppression is likely to be the most important toxicity (and dose limiting factor) to be observed in the clinical situation.

**Efficacy**

$^{90}$Yttrium is a precursor (to be used for radiolabelling purposes) for combination with other medicinal products consisting of a suitable linker (chelator) and a disease-specific carrier. **The $^{90}$Yttrium precursor is not to be given directly to patients.**

For this reason, concerning the clinical documentation (as defined in part 4 of the annex to the Directive 2001/83/EC of 6 November 2001): In the specific case and only in that case of precursors for radiolabelling purposes (such as Yttrium [$^{90}$Y] chloride) information relating to clinical efficacy obtained from the precursor *alone* is considered not to be relevant.

Appropriate information to support an indication as a radiolabelling agent has been included in this dossier, and this will be further supplemented by the results of relevant clinical efficacy and safety trials in the dossier of any carrier/linker molecule, which proposes to use $^{90}$Yttrium as radiolabel.

**Safety**

No original clinical safety studies were submitted in the application.

The safety of this product as a radiolabelling agent will be further supplemented by the results of relevant clinical efficacy and safety trials in the dossier of any carrier/linker molecule which proposes to use 90Yttrium as a radiolabel.

Appropriate information has been included in the summary of product characteristics for Yttrium [$^{90}$Y] chloride and should be included in the summary of product characteristics of the carrier medicinal product on the drug-drug interaction potential regarding chelating agents. EDTA may be used as an antidote in case that the $^{90}$Yttrium chloride precursor is erroneously given to patients.

**Recommendation**

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by concensus that the benefit/risk profile of Ytracis indicated 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.) was favourable and therefore recommended the granting of the marketing authorisation.