SCIENTIFIC DISCUSSION

1. Introduction

Yttriga is a solution of Yttrium [^{90}Y] chloride, which is a β-emitting radionuclide radio-pharmaceutical. Yttriga is a radio-pharmaceutical precursor solution for the *in vitro* radio-labelling of pharmaceutical substances (specific carriers), such as monoclonal antibodies, peptides or other chemical vectors for radio-immunotherapy. Yttriga is not be administered directly to patients.

Nuclear medicine imaging

In nuclear medicines imaging of scintigraphy, a source of photons (gamma) or positrons (beta) is attached to a specific compound and injected into the body. External detectors observe the emission of such radioactive elements. A typical image corresponds to an orthogonal projection of the density of radioactive elements, which is related to the metabolism of the radiopharmaceutical in the studied region (Mazziotta and Gilman 1992). Rotation of the gamma camera around the patient provides a set of projections that is fed onto tomographic algorithms similar to those used for x-ray computed tomography (CT). The result is a 3D volume of data tomoscintigraphy, or single photon emission CT (SPECT) (Lassen and Holm 1992). A more complex strategy studies the emission of positrons (positive electrons or antielectron): each emitted positron collides with an electron of the environment and gives rise to two high-energy photons that go in opposite directions. A ring of detectors set around the patient detects these two photons at very near instants. Thus, the associated events lie on a straight line between these two corresponding detectors. The intersection of such lines gives rise to a 3D region of emission from which a 3D image can be reconstructed. Such is the technique of positron emission tomography (PET) (Frost J.J. and Wagner H.N. 1990). Both SPECT and PET have relatively poor special resolution when compared with CT or MRI (typically a set of 64^3 or 128^3 voxels, each 2 to 10 mm^3, is obtained), but these methods provide functional information that is not available with other techniques (DeVita 2001).

Nuclear medicine therapy

Nuclear medicine therapy (radio-nuclide therapy) uses radioactive sources for the selective delivery of radiation to target organs or tumours. The therapeutic use of radio-isotopes has been developed in the mid 20th century, following the discovery of methods of production of artificial radio-nuclides. [^{131}I] has been used for the treatment of differentiated papillary or follicular thyroid carcinoma and [^{89}Sr] for palliation of bone pain from metastatic cancer. Potential new applications of radionuclide therapy in oncology reflect advances in antibody engineering (radio-immunotherapy), the identification of tumour antigen targets or the synthesis of peptide analogues (peptide therapy). These compounds are subsequently complexed with β- (or α-) emitting radio-nuclides in order to achieve an appropriate treatment through the delivery of a cytotoxic absorbed radiation dose to the target and prevent or minimise the toxicity for normal tissues. Up to now, two radio-labelled anti-CD20 antibodies have emerged and been used in the treatment of indolent B-cell lymphomas. In the EU, one anti-CD20 radio-immunotherapeutic agent has been approved for the treatment of patients with rituximab-relapse or refractory CD20+ follicular B-cell Non Hodgin's lymphoma ([^{90}Y] ibritumomab tiuxetan, Zevalin).

Radio-immunoconjugates

The toxic effects of radio-immunotherapy can extend over several cell diameters from the radiation source. Most radio-immunoconjugates do not require internalisation to be effective, and the cytotoxic effects do not require the presence of an intact, functional immune system. Radio-immunotherapy has been the most extensively studied immunoconjugate treatment strategy (DeVita 2001). In the past, most Radio-immunotherapy studies used iodine 131. Disadvantages of the use of ^{131}I are the unstable linkage to the carrier molecule, the weak energy of the therapeutic β- rays, and the emission of γ rays resulting in exposure of the environment to unwanted radiation. Improvement in chelation technology

has enabled the study of yttrium 90 conjugates. Yttrium 90 is preferred because of its high-energy β-emission, leading to a path length of up to 12 mm (mean of 5 mm) in tissues, its lack of volatility, and the relative ease and safety of its conjugation to antibodies and subsequent patient administration. This long track length enables the irradiation of cells which do not bind or accumulate the radio-labelled product. This crossfire effect is advantageous for therapy of larger tumors, where a homogeneous blood supply and therefore homogeneous activity distribution within the tumor cannot be achieved. Early studies of Radio-immunotherapy have shown that partial, short lived clinical responses can be achieved in some patients with advanced, solid tumors. Hematologic neoplasms are more responsive than are solid tumors. Bone marrow suppression is the common dose limiting toxicity. Lymphoma and leukemias remain the most sensitive tumor targets, presumably because of the intrinsic sensitivity to radiation and the relatively good access of radio-immunoconjugates to the malignant cells that comprise these neoplasms. The centrally approved radiopharmaceutical precursors solutions containing Yttrium [^{90}Y] chloride are Teryttrex and Ytracis.

Legal basis of the application

The applicant has submitted documentation covering quality and one non-clinical study report based on one rat biodistribution study, conducted to generate data for the evaluation of human internal radiation dosimetry, carried out by the applicant, and non-clinical and clinical bibliographic references. Where certain studies were replaced by bibliographical references, justifications have been given (see also 3.3 Non-clinical aspects, Discussion on Non-clinical aspects, and 3.4 Clinical aspects, Discussion on clinical aspects). This application has been submitted as full, mixed format, application, in accordance with Part II (7) of Annex I of Directive 2001/83/EC, as amended.

2. Quality aspects

Introduction

Composition

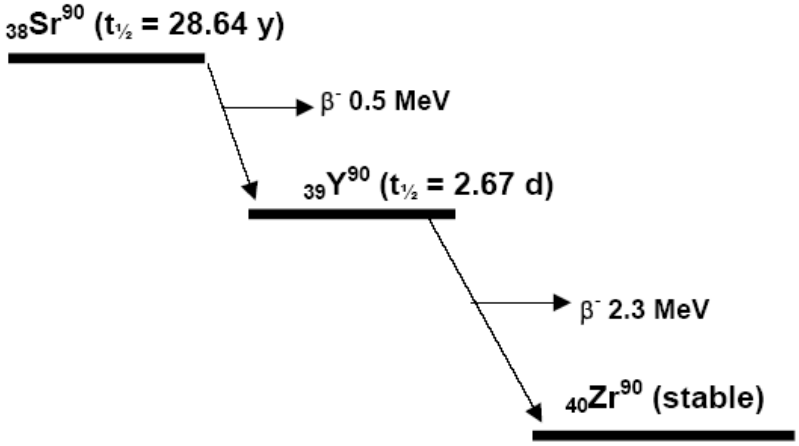
The product consists of a sterile solution of Yttrium (^{90}Y) chloride in dilute hydrochloric acid (0.04M) to minimise hydrolysis. 1 ml sterile solution contains 0.1-300 GBq Yttrium (^{90}Y) on the reference date and time corresponding to 0.005-15 micrograms of Yttrium [^{90}Y] (as Yttrium [^{90}Y] chloride). The theoretical specific activity is 20 GBq/microgram of Yttrium (^{90}Y).

Each vial contains 0.02-5 ml solution calibrated at a reference day/time. It is not possible to state a unique fixed total volume due to the fact that the quantity of the active substance is added to achieve a target activity per ml and per vial and this depends upon the specific activity of the 'bulk' active substance solution.

The primary packaging type is usual for radiopharmaceuticals. It consists of a glass vial with a PTFE faced chlorobutylrubber stopper or a silicon stopper, closed with an aluminium seal. The outer container is a lead container lined with synthetic material inside.

Drug Substance

Yttrium [^{90}Y] chloride is obtained by radioactive decay of strontium-90, present as strontium [^{90}Sr] nitrate. Yttrium-90 decays by emission of beta radiation with a maximum energy of 2.28 MeV to stable zirconium-90, with a half-life of 64.1 hours. The decay scheme of ^{90}Sr/^{90}Y is as follows:



- Manufacture

Yttrium [^{90}Y] chloride can be considered as the active substance of this product. It is produced by chemical separation from the mother nuclide [^{90}Sr] Strontium. The strontium [^{90}Sr] is allowed to decay to the daughter [^{90}Y]Yttrium. From this mixture, [^{90}Y]Yttrium is separated by extraction and is purified to remove trace quantities of [^{90}Sr]Strontium. The purified ^{90}Y material is then used for further processing.

The main objective of the manufacturing is to produce ^{90}Y of consistent purity with regard to radionuclidic impurities, metal impurities, organic impurities & anionic impurities. As far as radionuclidic impurities are concerned ^{90}Sr is the only radionuclidic impurity present from the production process. The Sr/Y ratio is ≤ 10^{-5} in the Yttrium (^{90}Y) chloride solution. The remaining radionuclidic impurities are those coming from the strontium material and are controlled by appropriate specifications for α- and γ-impurities. Metal impurities may arise from reagents, production vessels or starting materials. These will interfere with the radiolabelling process by competitive binding (chelation). Therefore it is important to keep the concentration of these contaminants at a very low level to improve radiolabelling with ^{90}Y.

- Specification

The specification for the active substance (bulk) contains relevant tests and limits as follows:

Table 1: Specification for the active substance (bulk)

Parameter	Test	Release specification
Appearance (glass vessel with dry (^{90}Y) YCl_3.The amount can only be determined by the radiation emitted, because of the small amount of material		
Identity ^{90}Y	Liquid scintillation counting	Corresponds to
γ-emitting impurities (given at a reference time point)	γ-spectrometry	< 1 x 10^{-4}Bq/ Bq ^{90}Y
^{90}Sr Concentration γ-emitting impurities (given at a reference time point)	strontium ^{90}Sr by precipitation and liquid scintillation counting	<1 x 10^{-5}Bq ^{90}Sr / Bq ^{90}Y
Radiochemical purity	DC	>99%
DTPA- binding	DC	>80%

- Stability

The chemical stability of the active substance is of limited importance in this case, although the radioactive decay characteristics have been defined so as to assign a suitably high concentration and specific activity for the bulk solution in order to reach the target for the finished product at the stated reference time.

Drug Product

- Pharmaceutical Development

Hydrochloric acid 0.04 M was chosen as solvent for Yttrium (^{90}Y) based on the following:
- the chloride anion was already present
- at low pH yttrium is present in ion form
- at the 0.04 M concentration the hydrochloric acid can easily be buffered

Yttrium (^{90}Y) chloride has been produced in lab-scale for more than 15 years. An large scale extraction process has been developed. The manufacturing method is a standard one consisting of three simple steps: solving, diluting, and dispensing. The product is sterilised using autoclaving and does not contain any microbial preservative.

Purity aspects of this radiolabelling agent which may have some impact on the clinical performance of the radiolabelled product have been identified:

Metallic impurities may arise from reagents, production vessels, starting materials. These will interfere with the radiolabelling process by competitive binding (chelation). Therefore it is important to keep the concentration of these contaminants at a very low level to improve radiolabelling with ^{90}Y.

Radionuclidic purity of the product (= % radioactivity of the radionuclide concerned/total radioactivity) is also a critical parameter as it may impact on radiotoxicity (resulting in aberrant radiation uptake of tissues).

Radiochemical purity (= % radioactivity of the radionuclide concerned present in the stated chemical form/total radioactivity of that nuclide) and chemical purity are also of influence on product performance and are controlled.

In order to ensure product quality a special test has been developed (DTPA binding) to detect any agents preventing ^{90}Y from being chelated by DTPA like metal ions, chelating organics etc.

The choice of the container is not unusual for sterile radioactive products and satisfactory specifications have been provided for the container materials.

- Manufacture of the Product

The drug substance is dissolved in 0.04 M HCl and aliquots are taken to determine the concentration of the nuclide in this solution. Depending on that concentration, the required amount of [^{90}Y]Yttrium solution is calculated taking into consideration the calibration day/time.

The calculated amount of solution will be injected in every vial followed directly with an amount of non-radioactive 0.04 M HCl needed to reach the required overall volume in that vial. The vials are then capped and sterilised in an autoclave. After sterilisation each vial is measured for the amount of [^{90}Y] Yttrium in an ionisation chamber and visual inspected for visible particles and appearance.

All critical process parameters have been identified and controlled by appropriate in process controls. The validation report from validation batches and 3 production scale batches demonstrates that the process is reproducible and provides a drug product that complies with the in-process and finished product specifications.

Product Specification

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.)

Table 2: Specification of the finished product

Parameter	Test	Release specification
Appearance		Clear, colourless solution
Identity of ^{90}Y	Liquid scintillation counting	corresponds
γ-emitting impurities (given at a reference point in accordance with customer requirements, measured in bulk material)	γ-spectrometry	<1 x 10^{-4}Bq / Bq ^{90}Y
^{90}Sr concentration (given at a reference point in accordance with customer requirements, measured in bulk material)	liquid scintillation counting after chemical processing	<1 x 10^{-5}Bq ^{90}Sr / Bq ^{90}Y
Volumes/weight determination (related to customer requirements)		0.02-5.0 ml (90-110%)
Activity /Activity measurements (related to customer requirements)		0.1-300 GBq (90-110%)
Chelatable metallic impurities /DTPA-bonding (measured in bulk material given at the day of production)	DTPA binding/DC	>80 % (corresponds to <2 pmol/3 kBq ^{90}Y)
Radiochemical purity	DC	>99%
Visual inspection of visible particles		Free of particles
Sterility	Ph.Eur	Sterile
Endotoxin concentration per Dose		< 30 E.U.

All tests included in the specification have been satisfactorily described and validated. Batch analysis data from 3 validation batches and 3 production batches have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- Stability of the Product

For the determination of the product quality at the end of the shelf life different activity levels of ^{90}Y (10, 50 and 300 GBq) were filled into the primary packaging (Both glass vials and stoppers intended for marketing were used). The parameters tested were activity, DTPA-binding, and ^{90}Sr content. Supporting stability data have also been presented from three batches with an activity of 2 GBq (at reference time and date) and a fill volume of 0.8 ml. The batches were tested on the production day and 2, 5, 9, 12, and 15 days later.

In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

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 for *in vitro* radiolabelling of carrier molecules, which will target a specific site (e.g. solid tumour) to allow accumulation and local irradiation. However there are defined quality characteristics, which the product meets in order to ensure efficient radiolabelling and batch-to-batch consistency. The manufacturing process is well described and controlled and appropriate specifications have been set. Given the short half-life of ^{90}Y stability issues are not as crucial as with other products intended to be stored for longer periods. However stability studies have been performed and show that the product remains within the specifications till the end of its shelf life.

3. Non-clinical aspects

Pharmacology

- Pharmacodynamics

The applicant has presented a review of the available pharmacodynamic data of Yttrium investigated *in vivo* (Pavelka, Meier-Ruge et al. 1975; Kutzner, Eckmann et al. 1985; Nakamura, Tsumura-Hasegawa et al. 1991; Nakamura, Tsumura-Hasegawa et al. 1991; Hirano, Kodama et al. 1993; Nakamura, Tsumura et al. 1993; Nakamura, Tsumura et al. 1997) in the format of literature references.

Histological studies
When administered intravenously to rats, ^{90}Y Yttrium citrate showed a high selective accumulation in bone. Bone marrow was the critical organ. A significant decrease of leukocytes and thrombocytes was observed at doses of 0.5 mCi (17.5 MBq)/kg and 2.0 mCi (74 MBq)/kg. A decrease of erythrocytes was also observed at 2.0 mCi (74 MBq)/kg. This dose being equivalent to a dose of 35-140 mCi (1.295-5.18 GBq) for a 70 kg human subject (Kutzner, Eckmann et al. 1985).
When administered intravenously to rats, cold Yttrium chloride (YCl_3) accumulated in the liver, the spleen and the bones. A 50 mg/kg dose induced spleen granulomas (Nakamura, Tsumura-Hasegawa et al. 1991; Hirano, Kodama et al. 1993). Doses higher than 200 µg induced the formation of a colloidal material composed of proteins and some minerals. This colloid was taken up by phagocytic cells in the liver and the spleen. Yttrium chloride was deposited in lysosomal inclusions of Kupffer cells and macrophages, with a half-time of the hepatic clearance of approximately 144 days. At a dose of 1 mg, a large amount of calcium was deposited in the liver and the spleen (i.e., more than 10 and 100 times the amount of calcium normally present in these organs, respectively) and a slight increase is observed in the lung and kidney.

Biochemical studies
Yttrium chloride administered intravenously increased the calcium concentration of liver, spleen and lung in rats. The distribution of calcium was similar to the distribution of Yttrium chloride in the liver. Higher sodium concentrations and lower potassium concentrations were observed in the rats treated. Zinc concentration in the liver increased slightly following the Yttrium chloride administration. No apparent changes were observed in magnesium and phosphorus (Nakamura, Tsumura *et al*. 1993). In the same study 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 hours after the injection was observed. In an other study (Hirano and Suzuki 1996) both aminotransferases were dramatically increased following the administration of 1 mg of Yttrium chloride intravenously. The authors explained these effects by the presence of colloidal form of Yttrium chloride in the blood, which triggers the activity of phagocyte cells in the liver and the spleen. Following the administration of high doses (9-10 mg/kg and 18-20 mg/kg), Yttrium were cleared from the blood within 24 hours. In the liver, the percentage of the dose of Yttrium found in the liver was maximal (71.9 % ± 2.9) from 8 hours to 2 days and decreased gradually. Changes in Ca concentrations in liver, spleen, and lung were in accordance with the Yttrium concentration observed (Nakamura, Tsumura et al. 1993).
The relevance of the observed effects has not been fully interpreted by the authors of the mentioned studies. The calcium mobilisation occurred rapidly after Yttrium chloride administration. The Yttrium chloride under its colloidal form accumulated preferentially in phagocytic cells in the liver and the spleen. The transitory increase of aspartate aminotransferase and alanine aminotransferase and the accumulation of calcium in the liver and spleen may have indicated that these organs are primary targets for high doses of Yttrium chloride administered intravenously (approximately 10^5 times the dose administered for radio-immunotherapy).

- Safety pharmacology program

Reference has been provided by the applicant (Stevenson, Daculsi et al. 1982) of one study in which the effect of 90Sr- and 90Y-treatment (2.5, 5, and 10 µCi/mouse) on the haemopoietic stem cell compartment and the immune status of mice has been investigated.
The kinetics of haemopoietic stem cells in femoral marrow, determined as colony forming units in spleen, CFU-s, were estimated. In all groups, dose-dependant increase in the percentage of CSF were observed during the five weeks post-incorporation. Towards the end of the period of observation the values remained subnormal.

- Pharmacodynamic drug interactions

No information regarding interaction of Yttrium chloride with other medicinal products has been provided. No animals data have been published. Free Yttrium (Y^{3+}) can complex chelating agents such as EDTA (ethylene diamine tetraacetic acid) which may modify its *in vivo* behaviour, leading to rapid renal elimination.

Pharmacokinetics

The applicant has presented a review of the published pharmacokinetics of Yttrium, providing data on the absorption (Deuber and Heim 1991), the distribution (Thomassen and Leicester 1964; Barnes, McClellan et al. 1972; Deuber and Heim 1991; Hirano, Kodama et al. 1993; Nakamura, Tsumura et al. 1993; Horovitz 2000), the metabolism (Kidman, Tutt et al. 1950; Thomassen and Leicester 1964; Hirano, Kodama et al. 1990) and the excretion (Barnes, McClellan et al. 1972) of Yttrium.

The pharmacokinetic properties of Yttrium depend on the dose administered (Nakamura, Tsumura-Hasegawa *et al*. 1991). Several pharmacokinetic studies using high doses of (cold) Yttrium [^{89}] chloride or low doses of either radioactive [^{90}Y] or non-radioactive [^{89}Y] 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 [^{90}Y] released after an *in vivo* dissociation of the radio-labelled immunoconjugate.

Depending on Yttrium [^{90}Y] chloride serum concentration, colloids of varying particle sizes are formed, which may explain marked differences in terms of biodistribution. Solutions of colloidal Yttrium chloride over a range of particle sizes prepared by varying the citrate/yttrium chloride ratio had different biodistribution patterns after intravenous injection in rabbits (Ramsden 1961). The large particles cleared rapidly and distribute mainly to the liver and to the spleen. The smaller particles cleared slowly and distributed to the bone and the bone marrow. The particles of intermediate size concentrated approximately after 18 hours equally in bone and liver. The concentration increased with the time in bone and decreased in other organs. Some Yttrium chloride remained at the site of injection (the exact particle sizes were not stated).

- Single-dose studies

  - *Pharmacokinetics of Yttrium administered at high doses*

A study (Nakamura, Tsumura-Hasegawa *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 occurred gradually in the faeces over a period of 7 days. No Yttrium chloride or rare earth elements were detected in the urine. A small quantity of Yttrium chloride was found in the kidney, in the pancreas and in the heart.
Yttrium chloride disappeared from whole blood within 4 hours. In the liver, the distribution 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 time. The distribution of Yttrium chloride in the bone increased gradually.

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

The tissue distribution and the subcellular localisation of Yttrium chloride were studied in rats (Hirano, Kodama et al. 1993). Yttrium chloride was administered at different dosages ranging from 0.1 to 2 mg/rat. 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 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 half-time of 144 days. At the concentrations tested, most of Yttrium in blood plasma was found in the colloids which are rapidly cleared and distributed as such in tissues.

In all the above mentioned studies, Yttrium injected at high dose by intravenous route accumulated primary in the liver and spleen. A dose dependent colloidal material was observed in the blood, composed of proteins and other minerals (calcium, strontium, sulphur, iron, phosphorus). This colloidal material was subsequently taken up by Kupffer cells and macrophages in the spleen.
Different elimination half-lives from the liver have been published (Hirano, Kodama et al. 1993; Nakamura, Tsumura et al. 1993) and were of 144 and 192 days, respectively. will be determined by their conjugation with the ligand and the therapeutic indication(s).
The absorption of cold Yttrium salts has been reported to be 0.05% of the dose taken up orally (Deuber and Heim 1991).

- *Pharmacokinetics of Yttrium administered at low doses*

In a study performed by (Durbin 1960) a small amount (the exact dose is not stated in the publication) of Yttrium [^{91}Y] chloride, a β-emitting isotope of Yttrium with a half-life equal to 58.51 days, was administered intramuscularly to rats. Four days after the administration Yttrium [^{91}Y] chloride distributed mainly in the bones (55.6 % of the initial dose) and in the liver (12.1 % of the initial dose).
A study on the distribution of Yttrium [^{88}Y] (0.5 mCi/mouse) administrated intravenously in mice (Gansow 1991) showed that, at 24, 48 and 168 hours, this isotope of Yttrium mainly accumulated in vertebrae, pelvis, femur, kidney and liver. The amount of Yttrium [^{91}Y] in bones was stable between 24 and 168 hours and was approximately equal to 20% of the injected dose per gram of bone in mice. Further kinetic studies indicated that Yttrium [^{90}Y] quickly reached the femurs (80% of the dose administered), from which the elimination half-time was 62 hours (i.e., close to the emission half-life of the isotope Yttrium [^{90}Y] which is equal to 64 hours). The uptake of Yttrium in the femoral marrow and muscle was small. Only 2 % and 1 % of the activity of the femoral bone were found in the femoral marrow and in the muscle, respectively. The half-life of Yttrium in the lung, after intratracheal instillation of 100 µg of Yttrium chloride to rats was 168 days (Hirano, Kodama et al. 1990).
In rabbits and dogs, Yttrium concentrated on bone surfaces (Jowsey, Owen et al. 1955). Yttrium was not found in either osteoid tissue or in areas of active calcification. In another study, 24 hours after an intraperitoneal injection of 500 pCi/kg of Yttrium [^{91}Y] chloride to puppies, Yttrium [^{91}Y] chloride accumulated on mineralised bone surfaces, mostly in the epiphyseal bone (Jowsey, Owen et al. 1955). 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.

In a study where rabbits were fed diets containing different amounts of Calcium, diet had no effect on the excretion in young animals (Kidman, Tutt et al. 1950).
In pregnant rats and cattle, Y-compounds did not cross the placental membrane, but were secreted into the milk (Luckey and Venugopal 1978).
The use of disodium calcium edetate ($CaNa_2EDTA$), to prevent or treat radio-myelosuppression, in case of Yttrium [^{90}Y] poisoning, has been investigated. In this study (Watanabe, Oriuchi et al. 1999), disodium calcium edetate was not able to complex Yttrium [^{90}Y] once fixed on the bones but chelated Yttrium [^{90}Y] before its deposition.

- Repeated-doses studies

In a repeated-dose study (reference not provided by the applicant) Yttrium chloride was given to rats in the peritoneum at 60 mg/kg every two days for 5 months. The maximum level of Yttrium in the femur was 100 times higher than the uptake of strontium given at a similar dose. Zirconium [^{90}] which is produced by the decay of Yttrium [^{90}Y], is also found in the alimentation. A standard diet is estimated to provide 3.5 mg of zirconium daily. Zirconium concentrates in erythrocytes and can be detected in several organs such as brain, kidney, liver, lungs, muscles, fatty tissue and lymph nodes. In the whole blood zirconium levels are between 0.012 and 1.25 µg/g (Berman and Eleanor 1980). These endogenous levels extremely high in comparison with the concentrations resulting from the decay of Yttrium [^{90}Y] chloride. The literature data suggest that repeated administrations lead to accumulation of Yttrium in the bone.

- Internal radiation dosimetry

Dosimetry of the labelled radiopharmaceutical depends on the pharmacokinetics of the carrier to be labelled. In order to generate data for the evaluation of the internal radiation dosimetry in humans, an evaluation of the internal radiation resulting from the free ^{90}Yttrium ($^{90}Y^{+3}$) that could be administered uncongugated or release from the protein conjugates has been submitted.
Female Sprague-Dawley rats were administered a single i.v. dose of Yttrium [^{90}Y] chloride at a nominal dose level of 15 MBq/kg bodyweight corresponding to 0.75 ng/kg of Y^{3+}. Organs and tissues were sampled at 5 minutes, 1, 6, 24, 96 and 360 hours and faeces and urine were collected throughout a period of 15 days.
At the end of the experiment, mean recovery was 23.8% in urine, 6.9% in faeces, 67.4% in organs and carcass and 0.2% in rinse water, corresponding to a total recovery of 98.38%. After 1 hour, the highest radioactivity was observed in the liver (9.3% of the administered dose/organ), followed by the kidneys (2.6%), femur (1.1%) and bone marrow (0.12%). Only part of the administered dose was excreted within 15 days. The highest recovery was observed in the carcass (56.5% of the administered dose/organ), followed by the skin (5.1%), femur (2.3%), liver (1.5%), kidneys (0.7%) and bone marrow (0.03%). Due to the short radioactive half-life of 64.1 hours of ^{90}Yttrium, only 1.4% of the administered radioactivity remained in organs 360 hours after administration. The elimination half-life of radioactivity from plasma was 24.9 hours.

The estimation of the human internal radiation dosimetry was performed in accordance with the Medical Internal Radiation Dose (MIRD) committee of the Society of Nuclear Medicine and the International Commission on Radiation Protection recommendations (ICRP).

Table 3: Organ dose (mGy/MBq injected) and effective dose (mSv/MBq):

Absorbed dose per unit activity administered (mGy/MBq)						
Organ	**Adult (70 kg)**	**15 years (50 kg)**	**10 years (30 kg)**	**5 years (17 kg)**	**1 year (10 kg)**	**Newborn (5 kg)**
Adrenals	7.23 E-01	1.09 E+00	2.53 E+00	3.62 E+00	7.23 E+00	2.17 E+01
Blood	4.20 E-02	6.29 E-02	1.47 E-01	2.10 E-01	4.19 E-01	1.26 E+00
Bone marrow	2.58 E+00	3.88 E+00	9.05 E+00	1.29 E+01	2.58 E+01	7.75 E+01
Brain	8.60 E-03	1.29 E-02	3.01 E-02	4.30 E-02	8.60 E-02	2.58 E-01
Carcass	5.82 E-01	8.72 E-01	2.04 E+00	2.91 E+00	5.82 E+00	1.75 E+01
Colon	2.30 E-02	3.46 E-02	8.06 E-02	1.15 E-01	2.30 E-01	6.91 E-01
Femur	7.76 E+00	1.16 E+01	2.72 E+01	3.88 E+01	7.76 E+01	2.33 E+02
Gastro-intestinal content	1.22 E-01	1.83 E-01	4.26 E-01	6.09 E-01	1.22 E+00	3.66 E+00
Heart	2.53 E-01	3.79 E-01	8.85 E-01	1.26 E+00	2.53 E+00	7.59 E+00
Ileum	1.16 E-02	1.74 E-02	4.06 E-02	5.81 E-02	1.16 E-01	3.48 E-01
Kidneys	2.35 E+00	3.53 E+00	8.24 E+00	1.18 E+01	2.35 E+01	7.06 E+01
Liver	1.27 E+00	1.91 E+00	4.46 E+00	6.37 E+00	1.27 E+01	3.82 E+01
Lungs	4.23 E-01	6.34 E-01	1.48 E+00	2.11 E+00	4.23 E+00	1.27 E+01
Ovaries	3.33 E-01	4.99 E-01	1.17 E+00	1.66 E+00	3.33 E+00	9.99 E+00
Pancreas	7.90 E-02	1.18 E-01	2.76 E-01	3.95 E-01	7.90 E-01	2.37 E+00
Sceletal muscle	6.12 E-04	9.17 E-04	2.14 E-03	3.06 E-03	6.12 E-03	1.83 E-02
Skin	1.02 E-01	1.53 E-01	3.58 E-01	5.11 E-01	1.02 E+00	3.06 E+00
Spleen	4.90 E-01	7.36 E-01	1.72 E+00	2.45 E+00	4.90 E+00	1.47 E+01
Stomach	6.47 E-02	9.70 E-02	2.26 E-01	3.23 E-01	6.47 E-01	1.94 E+00
Thymus	7.34 E-02	1.10 E-01	2.57 E-01	3.67 E-01	7.34 E-01	2.20 E+00
Thyroids	9.99 E-01	1.50 E+00	3.50 E+00	5.00 E+00	9.99 E+00	3.00 E+01
Urinary bladder	3.62 E-01	5.44 E-01	1.27 E+00	1.81 E+00	3.62 E+00	1.09 E+01
Uterus	1.51 E-02	2.26 E-02	5.28 E-02	7.55 E-02	1.51 E-01	4.53 E-01
Effective Dose (mSv/MBq)	**6.65 E-01**	**9.98 E-01**	**2.33 E+00**	**3.33 E+00**	**6.65 E+00**	**1.99 E+1**

Abbreviations: Bq = Bequerel (SI unit of radioactivity); Gy = Ggray (unit of absorbed dose); Sv = Sievert (unit for radiation dose).

In a 70-kg adult, the estimated absorbed doses were the highest in the femur, bone marrow, kidneys, liver, adrenals, thyroids, spleen and lungs.
The estimated effective dose to the whole body of a 70-kg adult resulting from an intravenously injected activity of 1 GBq was 665 mSv.

Toxicology

No original single dose or repeated dose toxicity studies were submitted.

- Single dose toxicity

Single-dose intravenous toxicity studies have been conducted in rats (Hirano, Kodama et al. 1993). Following the administration 0.1, 0.2, 0.5, 1 or 2 mg, 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 showed that phagocytes in the liver and spleen took up the colloidal material. The Yttrium in the liver was slowly cleared with a half-life of 144 days at a dose of 1 mg Yttrium/rat (see non-clinical Pharmacokinetics). Aspartate (AST) and alanine aminotransferase (ALT) activities in plasma were increased with a peak at 20 hour after the administration of 1 mg Yttrium/rat, and returned to their control values at 170 hour after the administration. 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 was found (Nakamura, Tsumura et al. 1993). Yttrium chloride given intravenously to rats increased calcium concentration in the liver, spleen and lung; a transitory increase of blood calcium concentration was observed but no changes were seen

in magnesium and phosphorus concentrations (Hirano, Kodama et al. 1993; Nakamura, Tsumura et al. 1993). At a dose of 1 mg Yttrium/rat (Hirano, Kodama et al. 1993), a significant amount of calcium was deposited in the liver (over 10-fold) and spleen (over 100-fold).

The median lethal dose (LD_{50}) values published for Yttrium in the literature (Deuber and Heim 1991) were in the range of 44 to 1710 mg/kg, depending on the administration mode, the animal model and the chemical form of the metal.

The following results were obtained from various sources of the literature (Horovitz 2000):
Table 4: Acute lethal toxicity doses (LD 50) of Yttrium salts in various species

Yttrium Salt	Species	Route of administration	LD_{50} (mg/kg)	Reference
YCl_3	Mouse	ip	58	Floersheim (1995)
	Guinea Pig	ip	85	Haley et al. (1962)
	Rat	ip	45	Kyker and Cress (1957)
$Y(C_6H_5O_7)$	Morse	ip	254	Luckey and Venugopal (1978)
	Gunea Pig	ip	44	
	Rat	ip	79	
$Y(NO_3)_3$	Frog	sc	350	Steidle and Ding (1929)
	Mouse	ip	175	Floersheim (1995)
	Mouse	ip	1710	Luckey and Venugopal (1978)
	Mouse	sc	1660	Steidle and Ding (1929)
	Rat	iv	20 – 30	Maxwell and Bischoff (1931)
	Rat	ip	350	Cochran et al. (1950)
	Rabbit	iv	515	Steidle and Ding (1929)
Y_2O_3	Mouse	ip	>3000	Floersheim (1995)
	Rat	ip	500	Cochran et al. (1950)

Abbreviations : ip = intraperitoneal; iv = intravenous; LD_{50} = Lethal Dose of Yttrium, given all at once, which causes the death of 50% of the group of test animals; sc = subcutaneous; $Y(C_6H_5O_7)$= Yttrium citrate; YCl_3= Yttrium chloride; $Y(NO_3)_3$ = Yttrium nitrate; Y_2O_3= Yttrium oxide.

Ten days after the administration of 12.5, 25, 37.5, 50, 75, 150 and 300 mg/kg of Yttrium in rats and mice, an LD_{50} values of 45 ± 2.1 mg/kg was found in rats and 88 ± 11.7 mg/kg in mice (Kyker and Cress 1957).

The median lethal dose (LD_{50}) for Yttrium and Zirconium after intraperitoneal administration to rats ranged from 117 to 395 mg/kg and 63 to 939 mg/kg, respectively (Cochran, Doull et al. 1950). Orally administered Zirconium showed LD_{50} values ranging from 990 to 2290 mg/kg.

The toxic effects of intraperitoneal injection of 140 mg of Yttrium nitrate in male Sprague-Dawley rats exposed to gamma rays has been investigated (Hartwig, Leffingwell et al. 1958). Rats receiving intraperitoneal injections of Yttrium nitrate plus whole body exposure to ionizing radiation evidenced a higher mortality than rats receiving either radiation or intraperitoneal injections of Yttrium nitrate alone. Subcutaneous injection of Yttrium nitrate caused abscess formation and subsequent epilation.

The results of a study comparing the toxicity of equivalent doses of Yttrium chloride, citrate and edentate complexes salts have been published (Graca, Davison et al. 1962). Toxic reactions were observed in mice and guinea pigs with doses from 25mg/kg to 500mg/kg. In general, the citrates were more toxic than the edetate complexes, and produced an acute passive congestion of lungs and liver within 4 hours after injection.

Yttrium oxide and Yttrium nitrate oral toxicity in Sprague-Dawley rats have been investigated (Lambert 1994). A limit dose of 5.0 g/kg was administered by gavage (50 % w/w solution in distilled water) to 10 fasted rats (200 - 300g) using 5 rats of each sex. The animals were observed for 14 days after dosing. The single acute oral LD_{50} of Yttrium oxide was found to be greater than 5.0 g/kg. However, the single acute oral LD_{50} of Yttrium nitrate was found to be less than 5.0 g/kg, with 100%

mortality by day 3. Toxic signs prior to death included lethargy, hunched posture, red nasal discharge and weight loss.

- Repeat dose toxicity

A 28 day repeated dose study was conducted in male and female rats which were administered doses of 0-1000 mg/kg/day of YCl_3 $6H_2O$ by oral gavage (Ogawa, Suzuki et al. 1992). The number of eosinophilic leukocytes increased in rats of both sexes dose-dependently. At a dose of 1000 mg/kg, hyperkeratosis in the forestomach of both sexes and eosinophilic leukocyte infiltration in the submucosa of the stomach of both sexes, erosion and dilatation of gastric gland of the glandular stomach in males, and swelling of the glandular stomach epithelium in females were observed. At doses higher than 200 mg/kg, a significant decrease of the serum cholinesterase activity was observed in females. Yttrium was accumulated mainly in the kidney but also in femur, liver and spleen, in a dose-dependent manner.
The relative chronic toxicity of 42 metal ions (mainly as chlorides), following i.p. injection to mice, was investigated by (Bienvenu, Nofre et al. 1963). The LD50 at 30 days was 44.5 ± 0.720 for sodium chloride and 0.66 + 0.012 for Yttrium chloride with relative toxicities of 1.0 and 67.4, respectively.
Intestinal adhesions, but no effect on growth, were observed when Yttrium chloride was administered i.p. to rats for 5 months (Bruce, Hietbrink et al. 1963).

- Genotoxocity

No genotoxocity studies have been performed by the applicant to evaluate the mutagenic potential of Yttrium.
Chromosome aberration has been observed in the peripheral blood lymphocyte after intraarticular injection of Yttrium-90 in patients (n = 20) treated for persistent synovitis of the knees. The net increase in dicentric abnormalities following the treatment was 0.011% per mCi and the total of damaged cells containing any unstable chromosome aberrations was 0.012% per mCi (Lloyd and Reeder 1978). Bacterial mutation assay was performed on *Salmonella typhimurium* strains and did not show mutagenic effects (Horovitz 2000). The mutagenic effects of Yttrium nitrate was studies on human and other mammalian somatic cells (Mu C.J. and Shi W.L. 1985). For concentrations between 2.5 - 266 mg/kg of the salts added to the culture medium of human peripheral blood lymphocytes, no differences from controls were observed. No change in the rate of chromosomal aberrations or the frequency of sister chromatid exchanges were observed. Cytogenetic damage in marrow cells of mice was quantified at various times up to 14 days after injection of ^{90}Y-labelled monoclonal antibodies. Aberrations, predominantly of the chromatid type, were elevated at 24 hours post injection and then declined over 14 days. Micronuclei numbers among polychromatic erythrocytes peaked 3 to 4 days after treatment and then declined exponentially but remained at higher than the expected levels (McFee, Robertson et al. 1994).
Results of other genotoxicity studies have been mentioned (Kaplan et al., 1973; Migalovskaya, 1971; Shevchenko, 1970; Brooks and McClellan, 1969).

- Carcinogenicity

No carcinogenicity studies have been performed by the applicant to evaluate the carcinogenic potential of Yttrium.
Carcinogenic effects of Yttrium radioisotopes have been observed in dogs (Horovitz 2000). Beagle dogs were exposed to doses of 1.700 to 2.800, 160 to 360, 76 to 270, and 26 to 190 rad per day of aerosols of ^{90}Y or ^{91}Y, attached to fused aluminosilicate particles. Seven years after exposure to aerosols of ^{90}Y or ^{91}Y, 5 dogs exposed to the ^{90}Y aerosol and 19 dogs exposed to ^{91}Y developed primary lung tumours. Hemangosarcoma were observed with $^{91}YCl_3$ and lymphosarcoma were observed with ^{90}Y-FAP (Muggenburg et al., 1986), squamous cell carcinoma of nasal cavity (Boecker et al., 1986) and tracheobronchial lymph node tumor (Hahn et al., 1986) were observed with $^{91}YCl_3$.
Contradictory publications regarding the carcinogenic effect of Yttrium have been provided (Schröder et al., 1971; Hutchenson et al., 1975).

- Reproductive and developmental studies

Reproductive functions
No data are available on the chemical toxicity of Yttrium on the reproductive function.

Embryo-foetal and perinatal toxicity
No teratogenic effects were caused by ^{90}Y on rabbits, whereas ^{90}Sr produced malformations of the long bones in mice and rats, as well as skeletal tail and eye defects in rats (Kidman, Tutt et al. 1951).
No teratogenic effects on rats and their offspring were caused by a mixture of REE nitrates (which included Scandium and Yttrium) at concentrations between 16 and 2000 mg/kg (Zong et al., 1992).

- Local tolerance

No studies have been performed by the applicant to evaluate the local tolerance of Yttrium.
Data on local tolerance have been published (Lambert 1994; Lambert 1994). Skin irritation test (0.5 g applied of Yttrium oxide to one intact and one abraded skin site and occluded for 24 hours) in rabbits did not show signs of dermal irritation. Eye irritation test in rabbits demonstrated Yttrium oxide is a mildly irritating agent to the eye. From investigations performed in rats, Yttrium nitrate has been classified as a moderate primary skin irritant and a severe irritating substance to the eye. Subcutaneous injection of Yttrium nitrate caused abscess formation and subsequent epilation and delayed wound healing in animals.

No toxicity studies have been provided to investigate the antigenicity, immunotoxicity, dependence, metabolites, or impurities of Yttrium.

Ecotoxicity/environmental risk assessment

An environmental risk assessment has been submitted. The report stated that no environmental risk associated with the solution of radioactive isotope [^{90}Y] Yttrium in 0.04 M HCl is expected, as only small volumes are to be handled (> 10 ml) and the medicinal product is to be used in authorised and trained institutions only.

Discussion on the non-clinical aspects

The applicant has conducted a review of the toxico-pharmacological studies for Yttrium (^{90}Y) available in the literature. The bibliographical references have been provided and discussed by the applicant. Consistent results have been shown across studies, and there is sufficient reassurance that the studies are reliable, and that the results are of general applicability. By choosing not to repeat certain animal studies, the applicant aimed to reduce the number of animals used for experimental purposes, and to limit animal testing to cases where there is a reasonable expectation that the result will extend the knowledge, with reference to Council Directive 86/609/EEC of 24 November 1986, as amended (EU Council 2003), and Council Decision 1999/575/EC (EU Council 23 March 1998). This is in agreement with recital 10, and the general principles of Annex I of Directive 2001/83/EC, as amended (EU Council 2001).

Pharmacology
Yttrium [^{90}Y] is a precursor to be used for radio-labelling purposes for combination with other medicinal products consisting of a suitable linker (chelator) and a disease-specific carrier. The main risk of using Yttrium [^{90}Y] chloride solution is the toxicity of the radiation from $^{90}Y^{3+}$ complex due to the emission of high-energy β rays. However, Yttrium chloride [$^{90}YCl_3$] is not intended to be directly administered to the patients and because of the low systemic exposure of Yttrium [^{90}Y], no pharmacodynamic effect is sought, neither for the radionuclide (unconjugated), nor for the (cold) Yttrium chloride itself. Primary or secondary pharmacodynamic effects are not considered likely or relevant for the application.
No pharmacodynamic drug interactions data have been submitted. Considering the available bibliographic data and considering that $^{90}YCl_3$ solution will not be injected directly to the patient, the absence of additional studies performed by the applicant were considered acceptable and therefore the

requirements in terms of non-clinical pharmacology documentation as set out in Directive 2001/83/EC, as amended (EU Council 2001), are considered fulfilled.

Pharmacokinetics
A single dose of Yttrium [^{90}Y] chloride injected intravenously was observed in plasma as a colloid and was taken up by the liver, the spleen and bones within a few hours. When injected through intramuscular, intraperitoneal or intravenous route at low dose in carrier-free form, Yttrium [^{90}Y] chloride accumulated mainly in bones. At low concentrations, Yttrium [^{90}Y] chloride was mainly adsorbed on the mineral parts of bones and/or is bound by strong electrostatic forces to carbamyl and sulphate groups of the bone tissue. There was almost no biological clearance from bones. The mechanisms of retention are unclear.
The uptake of Yttrium [^{90}Y] in the muscle and femoral marrow was low. In a study, the total urine and faeces elimination was 8 % to 10 % of the injected dose of Yttrium [^{91}Y], after the administration of a doses from 500 to 1000 μCi/kg to rabbits and dogs (Jowsey, Sisson et al. 1956). Pre-injection of chelators increased the elimination rate of Yttrium [^{90}Y] in the urine. Since Yttrium is intensively fixed on bones when administered at low doses, the bone uptake of Yttrium [^{90}Y] chloride may induce secondary myelosuppression.
Depending on the Yttrium [^{90}Y] chloride serum concentration, colloids of varying particle sizes were formed, which could explain marked differences of biodistribution. The different elimination half-lives observed from the liver (144 to 192 days) could also be explained by the differences between injected doses (10 mg and 1 mg), leading to the formation of dose-dependent colloid materials with different particle sizes and different elimination patterns.
The data observed in the literature in animal models are difficult to extrapolate to the extremely low dosages used in radionuclide therapy in human. At the concentrations used for radio-labelling purposes, the amount of radio-colloid formed as complex salts through interaction with plasma or blood proteins is likely to be extremely low.

Repeated-dose data available in the literature confirmed the pharmacokinetic properties of Yttrium observed from single-dose studies.
The quantities of Yttrium [^{90}Y] chloride administered during a treatment by radio-immunotherapy are such that interference with previous injections are unlikely, except for the radiobiological effects at the bone marrow levels which may be cumulative. This risk becomes lower considering that in standard radio-immunotherapies, the subsequent doses of Yttrium [^{90}Y] are generally given after the complete decay of the previous injection of Yttrium [^{90}Y].

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. The estimation of the human internal radiation dosimetry was performed in accordance with the MIRD/ICRP recommendations based on studies using female rats. The use of the MIRD approach was considered acceptable. In a 70-kg adult, the estimated absorbed dose was highest in the femur, bone marrow, kidneys, liver, adrenals, thyroids, spleen and lungs. The estimated effective dose to the whole body of a 70-kg adult resulting from an intravenously injected activity of 1 GBq was 665 mSv.
The tissue distribution data obtained form this study were in agreement with those reported in the literature with regard to the impact of the dose and the formation of colloids. The radiation dose received by the various organs following intravenous administration of an Yttrium (^{90}Y)-labelled medicinal product depends on the specific medicinal product being radio-labelled. It is recommended (see SPC section 5.4, Dosimetry) to refer to the radiation dosimetry of each different medicinal product following administration of the radio-labelled preparation, as stated in the SPC/PL of the particular medicinal product to be radio-labelled.

Overall, the knowledge about the pharmacokinetics of Yttrium [^{90}Y] as described in the literature was considered sufficient. Apart from the dosimetry study, the applicant did not carry out additional non-clinical pharmacokinetic studies with Yttrium. Additional non-clinical pharmacokinetic studies were considered unlikely to add any significant new knowledge about the pharmacokinetic profile of Yttrium, and were therefore not required. Thus, the requirements in terms of pharmacokinetic documentation as set out in Directive 2001/83/EC, as amended (EU Council 2001), are considered fulfilled.

Toxicology

Conventional single-dose studies with Yttrium have not been conducted by the applicant but results from available studies in the literature have been submitted as bibliographical references. Single-dose i.v. distribution and toxicology studies indicated that Yttrium is rapidly cleared from plasma and is mainly deposited in bone mineral. High dose target organ toxicity included the liver and the spleen. Each vial of the medicinal product contains a maximum dose of 300 GBq Yttrium [^{90}Y] with a theoretical specific activity of 20 GBq/μg, corresponding to a maximum quantity of 15 μg Yttrium [^{90}Y] per vial. Since the radioactive precursor is conjugated with the carrier molecule prior to it being administered to the patient, the maximum exposure to free Yttrium [^{90}Y] is well below 15 μg Yttrium [^{90}Y] (or 0.3 μg/kg in a 50-kg patient). Assuming a standard situation with a radio-incorporation rate of 90%, the maximum exposure to 0.03 μg/kg (30 ng/kg) of free Yttrium [^{90}Y] would be present in the formulation. This is substantially lower than the toxic dose levels reported in the literature where LD_{50}-values reported were 45 and 88 mg/kg for rat and mouse after intraperitoneal injection of Yttrium chloride.

Given the present state of scientific knowledge, and taking into account the low exposure in human to Yttrium and its degradation product, Zirconium, resulting from the radioactive precursor, additional single-dose toxicity studies with Yttrium were not required.

Conventional repeated-dose studies with Yttrium have not been conducted by the applicant. The results from available studies in the literature have been submitted as bibliographical references and show that Yttrium is absorbed from the gastrointestinal track and accumulated in the kidney, the femur, the liver and the spleen. It was highly irritative to the stomach mucosa when administered orally. Other studies from the literature, not submitted by the applicant, have investigated the chronic (> 5 months) intraperitoneal administration of Yttrium chloride in rabbits and the chronic (8 months) intratracheal administration of Yttrium oxide to rats (Haley 1965). After high doses of Yttrium administered to rats, granuloma formation in the spleen has been observed (Nakamura, Tsumura-Hasegawa et al. 1991). Publications on the toxicity of Zirconium (resulting from the decay of Yttrium [^{90}Y]) are also available but were not submitted (Berman and Eleanor 1980). Zirconium could lead to the immunological response of phagocytic cells in the liver and spleen.

At the recommended human dose, no systemic toxicity linked to Yttrium (as a non radioactive product) is expected. Since Yttrium [^{90}Y] will be given at very low concentrations the absence of original repeated toxicity studies in the dossier has been accepted. However, if free radioactive Yttrium [^{90}Y] is released, the toxicity will be related to the radiobiological effects of Yttrium [^{90}Y]. Moreover, the effect of Yttrium colloidal form accumulated in the liver and spleen, as well as the toxicity of the high doses of stable Zirconium are acknowledge.

Given the present state of scientific knowledge, and taking into account the information available in the literature, additional repeated-dose toxicity studies with Yttrium were not required.

Conventional genotoxicity and carcinogenicity studies have not been conducted by the applicant, in accordance with the requirements of Part III, paragraph 2.2 of Annex I of Directive 2001/83/EC, as amended (EU Council 2001). Adequate information have been provided in section 5.3 (Pre-clinical safety data) of the SPC. Results from studies available in the literature have been submitted as bibliographical references. Although the mutagenicity of the metal is unknown, the mutagenic potential of $^{90}Y^{3+}$ relates to the effects of radiations. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects (see SPC section 4.8, Undesirable effects). More recent data than those provided by the applicant have been published. ^{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.

The administration of 370 and 1,110 kBq to mice (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, Goddu et al. 2001). ^{90}Y also induced micronuclei in human peripheral blood lymphocytes (Mill, Wells et al. 1996). In mice, the survival of bone marrow granulocyte-macrophage colony-forming cells (GM-CFC) was reduced by intravenous administration of ^{90}Y citrate (Goddu, Howell et al. 1998).

No studies have been conducted to investigate the reproduction toxicity of Yttrium. No data are available on the chemical toxicity or the radio-toxicity of yttrium toward the reproductive function. Published data showed that a low fraction of orally administered Zirconium (0.23 g/kg/day in mice) was selectively fixed in the ovaries, inducing hypervascularisation one month after the end of treatment (Delongeas, Burnel 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 data is mentioned in the SPC (see section 5.3). Transfer of certain radioactive rare earth elements from mother to offspring *via* the placenta or the milk has been shown.

The local tolerance of Yttrium has not been investigated in specific non-clinical studies. This is in agreement with the requirements of Part III, paragraph 2.2 of Annex I of Directive 2001/83/EC, as amended (EU Council 2001).

No toxicity studies have been provided to investigate the antigenicity, immunotoxicity, dependence, metabolites, or impurities of Yttrium. The isotope ^{90}Y Yttrium is produced by separation from the mother nuclide ^{90}Sr by physico-chemical separation. This is the only isotope involved in the production process. The absence of study is in agreement with the requirements of Part III, paragraph 2.2 of Annex I of Directive 2001/83/EC, as amended (EU Council 2001).

Considering the assessment of environmental risks provided, the use of Yttrium [^{90}Y] chloride is associated with acceptable environmental risks, provided that the current regulations related to the handling and disposal of radiopharmaceuticals are followed. Radio-pharmaceuticals should be received, used and administered, only by authorised persons, in designated clinical settings. Receipt, storage, use, transfer and disposal are subject to the regulations and appropriate licences of the competent authorities. The user should prepare radio-pharmaceuticals 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. Appropriate information has been included in section 4.4 (Special warnings and special precautions for use) and 6.6 (Instructions for use and handling) of the SPC.

In conclusion, the knowledge about the pharmacology and the toxicology of Yttrium, based on available studies in the literature and the documentation submitted by the applicant, is considered sufficient. Additional non-clinical toxicology studies are not expected to provide any significant new information about the safety profile of Yttrium, and are therefore not required. The requirements in terms of pharmacology and toxicology documentation as set out in Directive 2001/83/EC, as amended (EU Council 2001), are considered fulfilled.

4. Clinical aspects

Introduction

Since [^{90}Y]Yttrium is to be exclusively used for the *in vitro* radio-labelling of pharmaceutical substances, such as monoclonal antibodies, peptides or other substrates for radio-nuclide therapy, [^{90}Y]Yttrium should not be administered directly to patients. Clinical information generated from clinical studies using on the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes, as stated in Part III, paragraph 2.2 of Annex I of Directive 2001/83/EC, as amended (EU Council 2001). Therefore, no original studies on the clinical efficacy of [^{90}Y]Yttrium have been performed by the applicant.
However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules are required in the Regulation (EU Council 2001). An overview of the published experience of ^{90}Y showing therapeutic utility in targeted *in vivo* radiotherapy has been presented. GLP compliance has not been reported in the publications reviewed.

Documentation submitted on clinical utility

Pharmacology
Clinical pharmacology for different Yttrium [^{90}Y]-labelled products published in the literature have been submitted. These publications referred to studies conducted with radio-labelled antibodies (Rosenblum, Kavanagh et al. 1991; Waldmann, White et al. 1995; Alcindor and Witzig 2002; Johnson, Cole et al. 2002), radio-labelled peptides (Leimer, Kurtaran et al. 1998; Paganelli, Grana et al. 1999; Valkema, De Jong et al. 2002; Waldherr, Pless et al. 2002; Bushnell, O'Dorisio et al. 2003) or pre-targeted radio-immunotherapy (Cremonesi, Ferrari et al. 1999; Paganelli, Grana et al. 1999; Knox, Goris et al. 2000).

Poor chelation, product gradient or protein or peptide digestion may be responsible for the release of unconjugated Yttrium [^{90}Y] *in vivo*.
From the clinical experience in the preparation of ibritumomab tiuxetan using a radio-labelling kit, it has been shown that, among 402 out of 410 doses prepared, the radiochemical purity was 97.9% $\pm$ 3.4 % (Chinn 2000). Clinical release specification was determined by radiochemical purity testing.
The amount of free [^{90}Y] released after injection was negligible in the case of injection of [^{90}Y]-DOTA-biotin, but was 5,6 % ± 2,5 % of the injected dose in the case of injection of [^{90}Y]-DTPA-biotin (Cremonesi, Ferrari et al. 1999). The authors stated that small fractions of free [^{90}Y] from incomplete radio-labelling could significantly contribute to the red marrow dose (3,26 mGy per MBq of free [^{90}Y]).
Indirect evidence of the uptake of [^{90}Y] by bone was shown in patients with ovarian cancer receiving intra-peritoneal [^{90}Y] labelled monoclonal antibody HMFG1 (Stewart, Hird et al. 1990).

Efficacy
An overview of the published experience of ^{90}Y, showing therapeutic utility in targeted *in vivo* radiotherapy, has been presented. To date, one randomized phase III study, with ^{90}Y Zevalin (authorised in the EU *via* the centralized procedure as Zevalin), a ^{90}Y-labelled anti-CD20 monoclonal antibody, developed for the treatment of low-grade non-Hodgkin's lymphoma (NHL) has been published. The other presented studies using ^{90}Yttrium-labelled compounds were phase I studies, or summarized observations of case reports.

Zevalin contains ibritumomab, an IgG1 kappa immunoglobulin which reacts specifically with the CD20 antigen found on the surface of normal and malignant B lymphocytes, targets of its cytotoxicity. Ibritumomab is conjugated *via* a linker to the chelating agent MX-DTPA (tiuxetan), which securely chelates the radioisotope yttrium-90. Tiuxetan is stably bound to the antibody via a covalent, urea type bond. Ibritumomab tiuxetan achieves selective targeting CD20+ cells, which are inherently sensitive to radiation. The radionucleide yttrium-90 emits pure high-energy beta radiation with a local tissue penetration (5 to 10 mm) and effect. This regimen combines the antibody-based tumour cell killing with rituximab with an antibody based radioimmuno-therapy and thus further tumor-cell killing, but with a different mechanism of action (radiation).
In a randomised controlled trial, 143 patients with relapsed or refractory low-grade, follicular, or transformed CD20+ NHL were studied. The treatment with ^{90}Y ibritumomab tiuxetan was preceded by two infusions of rituximab, an unlabelled anti-CD20 antibody, to optimise the biodistribution of the radiolabelled antibody. After pre-treatment, patients were randomised to treatment with Zevalin (0.4 mCi/kg, n = 73) *versus* standard therapy with rituximab (375 mg/m^2 i.v. weekly in four doses, n = 70). The overall response rate (ORR), primary efficacy endpoint, for the patients in the ^{90}Y ibritumomab tiuxetan group was 80% *versus* 56% in the rituximab group (p = 0.002). Complete response (CR) rates were 30% and 16% in the ^{90}Y Yttrium ibritumomab tiuxetan and rituximab groups, respectively (P = 0.04). An additional 4% achieved an unconfirmed CR in each group. Kaplan-Meier estimated median duration of response was 14.2 months in the ^{90}Y Yttrium ibritumomab tiuxetan group *versus* 12.1 months in the control group (P = 0.6), and time to progression was 11.2 *versus* 10.1 months (P = 0.173) in all patients. Durable responses of 6 months were 64% vs. 47% (P = 0.030).

A number of other Yttrium [^{90}Y] labelled monoclonal antibodies or its fragments, for which clinical trials have been reported include, among others, the monoclonal antibody against leukocyte-DR-antigen (DeNardo, O'Donnell et al. 2000), the humanised anti-CD22 monoclonal antibody

epratuzumab (Linden, Tennvall et al. 2001; Sharkey, Brenner et al. 2003), the glycoprotein TAG-72 for intra-peritoneal therapy of ovarian cancer (Alvarez, Huh et al. 2002). The clinical efficacy of radio-immunotherapy was also investigated in Hodgkin's disease using ^{90}Y anti-ferritin immunoglobulin (Vriesendorp, Herpst et al. 1991; Bierman, Vose et al. 1993; Herpst, Klein et al. 1995), metastatic carcinoma-embryonic-antigen (CEA)-producing malignancies using ^{90}Y Yttrium labelled CEA (Wong, Chu et al. 2000) or Non-Hodgkin's Lymphoma using ^{90}Y -DOTA-hLL2 (Griffiths, Govindan et al. 2003).

In addition, clinical studies have investigated the therapeutic efficacy of ^{90}Y when conjugated to peptides in patients with neuroendocrine tumours using ^{90}Y Dodecaetetraacetic acid-Phe1-Tyr3-octreotide, ^{90}Y -SMT 487 (Bushnell, O'Dorisio et al. 2003), progressive neuroendocrine gastro-enteropancreatic and bronchial tumours using ^{90}Y Yttrium-DOTATOC (Otte, Herrmann et al. 1999; Schumacher, Hofer et al. 2002), and cancers expressing somatostatin receptors using ^{90}Y Yttrium-DOTATOC (Otte, Herrmann et al. 1999; Paganelli, Grana et al. 1999; Schumacher, Hofer et al. 2002; Valkema, De Jong et al. 2002; Waldherr, Pless et al. 2002; Bushnell, O'Dorisio et al. 2003). From these studies using ^{90}Y labelled peptides, a disease stabilisation or partial response was observed in patients with somatostatin receptor-positive tumours, who had no other treatment option.

To enhance the therapeutic efficacy of radio-immunotherapy, the tumour is pre-targeted with an antibody construct that has affinity for the tumour-associated antigen on one hand and for a radio-labelled hapten on the other. The antibody is administered first; after clearing from circulation, the radio-labelled hapten is injected. Two main approaches in this strategy can be distinguished: pre-targeting based on the avid interaction of streptavidin or avidin and biotin, and pre-targeting based on the use of bispecific antibodies. No clinical data are published on radio-immunotherapy based on bispecific antibodies using [^{90}Y]Yttrium as label.

Dosimetry and pharmacokinetics data have been published in cancer patients using a three-step radio-immunotherapy with Yttrium [^{90}Y] labelled biotin (Cremonesi, Ferrari et al. 1999). Data on a three-step therapy of high grade gloomy with Yttrium [^{90}Y] labelled biotin were reported (Paganelli, Grana et al. 1999).
Pre-targeting consisting in a murine monoclonal antibody NR-LU-10/streptavidin followed by a single dose of biotinylated Yttrium [^{90}Y]-DOTA 72 hours later has been used for treatment of colon cancer (Knox, Goris et al. 2000) and adenocarcinomas (Breitz, Weiden et al. 2000). A study has investigated the pre-targeted radio-immunotherapy in patients with non-Hodgkin`s lymphoma using the anti-CD20 antibody C2B8 (rituximab) conjugated to [^{90}Y] labelled streptavidin (Weiden, Breitz et al. 2000). The reported results of these studies suggested that higher activities than those achievable with conventional radio-immunoconjugates can safely be administered using pre-targeting, although the results were preliminary.

Safety
Published reports of the clinical safety of different Yttrium [^{90}Y] labelled products have been submitted.
Possible adverse events are mainly dependent on the specific product to be radio-labelled. Known side-effects of free Yttrium [^{90}Y] are an increased bone marrow toxicity and haematopoietic stem cell damage (Hnatowich, Mardirossian et al. 1991; Herpst, Klein et al. 1995; Cremonesi, Ferrari et al. 1999; Kahn, Austin et al. 1999; Wiseman, Gordon et al. 2002; Witzig, Gordon et al. 2002). Administration of 0.4 mCi/kg of [^{90}Y]-ibritumomab tiuxetan lead to a significant yttrium-90 radiation dose which was expected to lead to the standard radiation effects particularly on dividing cells. Since the radiation source was bound to the B-cell antibodies, and therefore to B-cells, the main radiation effect was expected to occur in lymphomas, bone marrow, lymphoid tissues and organs containing lymphoid cells.

The grade of the toxicity was dependent of the injected activity, which has been investigated in dose escalating studies. In 179 patients treated with Yttrium [^{90}Y]-ibritumomab, dosimetry and pharmacokinetics of Yttrium [^{90}Y] did not correlate with toxicity (Wiseman, Leigh et al. 2003). The therapeutic administered dose ranged from 7.4 -15 MBq/kg Yttrium [^{90}Y]-ibritumomab. The observed toxicity was primarily hematological, transient and reversible. The author concluded that patients with

adequate bone marrow reserve and less than 25% bone marrow involvement by NHL could be treated safely with Yttrium [^{90}Y]-ibritumomab on the basis of a fixed weight adjusted dosing schedule.
Among five patients with advanced somatostatin receptor positive tumours, who received a cumulative dose of more than 7400 MBq/m^2 of ^{90}Y-DOTA-D-Phe-Tyr-octreotide (DOTATOC), four patients developed renal toxicity; two of these patients showed stable renal insufficiency, two required haemodialysis, two exhibited grade 3 anaemia and thrombopenia, grade 2 and 4, respectively (Otte, Herrmann et al. 1999).
During pre-targeting regime using ^{90}Y-DOTA-biotin, transient grade 1/2 non-hematological toxicity was observed (nausea/vomiting, diarrhea, elevation of liver function tests, fever, chills, and azotemia). Mild and transient hematological toxicity was also observed. Patients who received 30 to 50 mCi/m2 of 90Y experienced transient grade 3 hematological toxicity. No grade 4 hematological toxicity was observed (Weiden, Breitz et al. 2000).
In a dose escalating trial, most patients (75%) experienced low hematological toxicity (0-2) consisting of thrombocytopenia or thrombocytopenia plus neutropenia. At an activity level of 2,96 GBq/m2 more than 30% of patients developed grade 4 hematological toxicity (Paganelli, Grana et al. 1999).

Dosimetry / Overdosage
The dosimetry estimates have been based on a rat distribution study and the calculations have been done in accordance with MIRD/ICRP 60 recommendations. Time-points for measurements were 5 min, 1, 6, 24, 96 and 360 hours. The effective dose to a 70 kg adult resulting from an intravenously injected activity of 1 GBq was 665 mSv.

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 Yttriga has been evaluated (see non-clinical pharmacokinetics and discussion on clinical utility).

Discussion on clinical utility

Pharmacology

^{90}Yttrium chloride, as a radiopharmaceutical precursor solution, is not intended for direct administration to patients but is to be used as precursor to radiolabel targeting agents. These targeting agents, e.g. monoclonal antibodies, peptides or other substrates are highly specific to the targeted sites. The biodistribution of ^{90}Yttrium is specific to the carrier to be radio-labelled and the radiation dose received by the organs, following intravenous administration of an Yttrium (^{90}Y)-labelled medicinal product dependents on the specific radio-labelled medicinal product. Information on radiation dosimetry of individual medicinal products, following administration of the radio-labelled preparation, can be found in the product information of the individual medicinal products to be radio-labelled.
Unconjugated ^{90}Yttrium may be released *in vivo* due to poor chelation, product gradient or protein or peptide digestion. The radiochemical purity was 97.9% $\pm$ 3.4% in one published study on pharmacodynamics of free Yttrium [^{90}Y] resulting from unstable binding. The expected unbound Yttrium [^{90}Y] activity should therefore be less than 3% at the time of injection (impurities were not specified).
The low amounts of free ^{90}Yttrium present in the final product are expected to accumulate primarily in the bones, with a small part being retained in the liver and spleen. The radioactivity in the bones may also cause irradiation of the bone marrow, which may lead to hematological toxicity.
In agreement with the recommendation of the requirements of Part III, paragraph 2.2 of Annex I of Directive 2001/83/EC, as amended (EU Council 2001), the applicant did not carry out specific patient pharmacology studies on ^{90}Yttrium, and an adequate description of the pharmacokinetics of free ^{90}Yttrium was provided, based on relevant bibliographic data.

Efficacy

Since [^{90}Y] Yttrium is to be exclusively used for the *in vitro* radio-labelling of pharmaceutical substances, such as monoclonal antibodies, peptides or other substrates for radio-nuclide therapy, [^{90}Y]Yttrium should not be administered directly to patients. In agreement with the recommendation of the requirements of Part III, paragraph 2.2 of Annex I of Directive 2001/83/EC, as amended (EU

Council 2001), no original studies on the clinical efficacy of [^{90}Y]Yttrium have been performed by the applicant.
To date, one randomized phase III study, with ^{90}Y Zevalin, a ^{90}Y-labelled anti-CD20 monoclonal antibody [see European Public Assessment report (EPAR) of Zevalin (EMEA website 2004)], developed for the treatment of low-grade non-Hodgkin's lymphoma (NHL) has been authorized, supporting the clinical utility of the radionucleide ^{90}Y. As required in the Regulation (EU Council 2001), the information provided were considered satisfactory to support the demonstration of the clinical utility of the radio-pharmaceutical precursor to be used only for the radio-labelling of carrier molecules, which have been specifically developed and authorised for radio-labelling with this radionuclide (see section 4.1 of the SPC). Yttriga is only to be used by specialists with the appropriate experience (see section 4.2 of the SPC). There is no therapeutic indication of [^{90}Y]Yttrium *per se*, as a precursor, and relevant non-clinical and clinical information relating to the clinical use of the labelled product are to be provided in the dossier of the carrier. The quantity of Yttriga required for radiolabelling and the quantity of Yttrium (^{90}Y)-labelled medicinal product that is subsequently administered will depend on the medicinal product radio-labelled and its intended use (see section 4.2 of the SPC). Yttriga is intended for *in vitro* labelling of medicinal products which are subsequently administered by the approved route (see section 4.2 of the SPC). For information concerning interactions associated with the use of Yttrium (^{90}Y)-labelled medicinal products should be obtained from the SPC/package leaflet of the medicinal product to be radio-labelled (see section 4.5 of the SPC, Interaction with other medicinal products and other forms of interaction).

Safety

No original studies on the clinical safety of [^{90}Y] Yttrium have been performed by the applicant. This was in agreement with the recommendation of the requirements of Part III, paragraph 2.2 of Annex I of Directive 2001/83/EC, as amended. *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. An important feature of the Yttrium [^{90}Y] labelled medicinal products will be *in vivo* stability of the carrier-radiolabel complex and the occurrence of free Yttrium [^{90}Y]. Free Yttrium [^{90}Y] is incorporated in a solid-phase bone matrix and may produce, due to the long beta particle path length, bone marrow toxicity. The development of stable chelator linkers is therefore important for medicinal products intended to use Yttrium [^{90}Y] as radiopharmaceutical precursor.
An overview of the available data on the safety of [^{90}Y] Yttrium form the literature has been presented. In the publications provided, bone marrow toxicity, 2 to 4 weeks post-treatment, was transient (recovery within 8 to 10 weeks). Both in Hodgkin's disease and NHL, haematological toxicity was best correlated with the dose of [^{90}Y] Yttrium (mCi) ^{90}Y administered per kg of bodyweight as compared to total dose (mCi) or dose per body surface (mCi/m$^{2)}$. Furthermore, haematological toxicity was correlated with previous bone marrow damage or pre-treatment platelet count in Hodgkin's disease and NHL. 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. 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 (see SPC section 4.8, Undesirable effects). Possible side effects following the intravenous administration of Yttrium (^{90}Y)-labelled a medicinal product prepared by radiolabelling with Yttriga, will be dependent on the specific medicinal product being used, as specified in the SPC of the medicinal product to be radio-labelled. It is recommended that 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 (see SPC section 4.4, Special warnings and special precautions for use). As radiopharmaceuticals, Yttriga should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements and particular care should be taken when administering radioactive medicinal products to children and adolescents (see SPC section 4.4). Effects on ability to drive and to use machines following treatment by Yttrium (^{90}Y)-labelled medicinal products will be specified in the Summary of Product Characteristics/package leaflet of the medicinal product to be radio-labelled (see SPC section 4.7, Effects on ability to drive and use machines).

- Safety in special populations

Particular care should be taken when administering radioactive medicinal products to children and adolescents (see section 4.4 of the SPC, Special warnings and special precautions for use). Before administration of a Yttrium (^{90}Y)-labelled medicinal product pregnancy has to be excluded (see section 4.6, Pregnancy and lactation). Yttriga is contraindicated in case of established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3 of the SPC, Contraindications).
In case of pregnancy, alternative techniques which do not involve ionising radiation should always be considered. Before administering a radioactive medicinal product to a mother who is breast feeding, consideration should be given to whether the investigation 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 (see SPC section 4.6). Yttriga is also contraindicated in case of hypersensitivity to Yttrium (^{90}Y) chloride or to any of the excipients. Regarding contraindications or information concerning the use of a Yttrium (^{90}Y)-labelled medicinal in pregnancy and lactation to particular Yttrium (^{90}Y)-labelled medicinal products prepared by radio-labelling with Yttriga, it is recommended that (see SPC section 4.3 and 4.6), information is obtained from the SPC/package leaflet of the particular medicinal product to be radio-labelled.

- Overdosage

Situation of accidental ingestion or injection of the radioisotopes in human has been considered. From the decay of ^{90}Yttrium, stable Zirconium is formed. As the maximum administered amounts of Yttrium and Zirconium are expected to be less than 59 ng (assuming a dose to be administered of 0.4 mCi/kg with a specific activity of 0.54 mCi/ng ^{90}Yttrium), metal induced toxicity is not expected in the long term. However, in case of accidental administration of the total amount of a vial containing 300 GBq (approximately 8 Ci) ^{90}Yttrium administered i.v. as free ^{90}Yttrium, would lead to serious health concerns (hematological ablation) and death. The applicant has however specified that the maximal batch size produced for the medical practice market is 2 GBq (validation batch vials were in the range of 1.2-1.6 GBq, i.e., 0.060-0.090µg ^{90}Yttrium). The accidental ingestion or injection of such a vial, would lead to severe but reversible radiation-induced haematological toxicity (bone marrow toxicity and haematopoetic stern cell damage) and would not result in significant metal toxicity.
Appropriate information has been included in section 4.9 (overdose) of the SPC for Yttrium [^{90}Y] chloride and should be included in the SPC of the carrier medicinal products on the drug-drug interaction potential section regarding chelating agents. In case of an inadvertent administration of Yttriga, the radio-toxicity for the patient must be reduced by immediate (i.e. within 1 hour) administration of preparations containing chelators like Ca- DTPA (trisodium calcium diethylenetriaminepentaacetate) or Ca-EDTA (calcium disodium ethylenediaminetetraacetate) in order to increase the elimination of the radionuclide from the body. 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). In the SPC (section 4.9), it recommended that 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. Preparation of Ca-DTPA and Ca-EDTA must be available in medical institutions, which use Yttriga for labelling of carrier molecules for therapeutic purposes. 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.

a. Overall conclusions, benefit/risk assessment and recommendation

Quality

Overall the quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC.

Non-clinical pharmacology and toxicology

Non-clinical published data showed that unconjugated Yttrium (^{90}Y) chloride accumulates in bones and radiation-induced myelosuppression was considered as the most important toxicity (and dose limiting factor) to be observed in clinical situation. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. Based on available studies in the literature and the clinical experience with radio-pharmaceutical precursors for radio-labelling purposes, additional non-clinical toxicology studies were not required to provide any significant new information about the safety profile of Yttrium. The essential data derived from pre-clinical studies, which pertain to human risk, have been incorporated into the Summary of Product Characteristics.

Clinical utility

^{90}Yttrium is a radio-pharmaceutical precursor, intended solely for radio-labelling purposes for combination with other medicinal products such as monoclonal antibodies, peptides or other substrates for radio-nuclide therapy. As a precursor, [^{90}Y]Yttrium is not to be given directly to patients. Published experience of ^{90}Y showed the therapeutic utility in targeted *in vivo* radiotherapy. Appropriate information to support an indication as a radio-pharmaceutical precursor for radio-labelling has been provided. Relevant non-clinical and clinical information related to the clinical use of the carrier molecules, which have been specifically developed and authorised for radio-labelling with this radionuclide, are to be included in the SPC of the carrier molecules.

Dose-dependent haematological toxicity, mainly related to haematopoietic stem cell damage, was the principal identified side effect of Yttrium [^{90}Y]. The myelotoxicity is mainly due to direct stem cell targeting by the radiopharmaceutical rather than irradiation coming from non-conjugated Yttrium (^{90}Y) accreting into bone. The minor potential contribution of free Yttrium-90 to bone marrow toxicity has been considered as unlikely taking into account the development of new stable chelator linkers.
As for all radioactive products, the radiation dose resulting from the therapeutic exposure may result in higher incidence of cancer and mutations. Exposure to ionising radiation must be justifiable on the basis of likely clinical benefit.

Benefit/risk assessment

There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.
Clinical data are not relevant in support of the authorisation procedure for this precursor. However, sufficient appropriate literature reports on Yttrium (^{90}Y) chloride labelled monoclonal antibodies and peptides support the use of Yttrium (^{90}Y) chloride labelled molecules in humans.
Dosimetry has been calculated from a rat study using the MIRD/ICRP 60 recommendations.
In conclusion Yttriga has a positive benefit/risk ratio to be used only for the radio-labelling of carrier molecules, which have been specifically developed and authorised for radio-labelling with this radionuclide. No additional pharmacovigilance activities or additional risk minimisation measures will be required other than those stated in the SPC/PL recommendations.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk ratio of Yttrium [^{90}Y] chloride [YCl_3] sterile solution AEA Technology, as a radio-pharmaceutical precursor, not intended for direct use in patients, to be used only for the radio-labelling of carrier molecules, which have been specifically developed and authorised for radio-labelling with this radionuclide was favourable and therefore recommended the granting of the marketing authorisation.

References

Alcindor, T. and T. E. Witzig (2002). "Radioimmunotherapy with yttrium-90 ibritumomab tiuxetan for patients with relapsed CD20+ B-cell non-Hodgkin's lymphoma." Curr Treat Options Oncol **3**(4): 275-82.

Alvarez, R. D., W. K. Huh, et al. (2002). "A Phase I study of combined modality (90)Yttrium-CC49 intraperitoneal radioimmunotherapy for ovarian cancer." Clin Cancer Res **8**(9): 2806-11.

Barnes, J. E., R. O. McClellan, et al. (1972). "Toxicity in the dog of inhaled 90 Y in fused clay particles: distribution, retention kinetics, and dosimetry." Radiat Res **49**(2): 416-29.

Berman and Eleanor (1980). Toxic Metals and their Analysis. London.

Bienvenu, P., C. Nofre, et al. (1963). "[The comparative general toxicity of metal ions. Relation with the periodic classification.]." C R Hebd Seances Acad Sci **256**: 1043-4.

Bierman, P. J., J. M. Vose, et al. (1993). "Yttrium 90-labeled antiferritin followed by high-dose chemotherapy and autologous bone marrow transplantation for poor-prognosis Hodgkin's disease." J Clin Oncol **11**(4): 698-703.

Breitz, H. B., P. L. Weiden, et al. (2000). "Clinical optimization of pretargeted radioimmunotherapy with antibody-streptavidin conjugate and 90Y-DOTA-biotin." J Nucl Med **41**(1): 131-40.

Bruce, D. W., B. E. Hietbrink, et al. (1963). "The Acute Mammalian Toxicity of Rare Earth Nitrates and Oxides." Toxicol Appl Pharmacol **44**: 750-9.

Bushnell, D., T. O'Dorisio, et al. (2003). "Evaluating the clinical effectiveness of 90Y-SMT 487 in patients with neuroendocrine tumors." J Nucl Med **44**(10): 1556-60.

Chinn, P. M., RA. Wiseman, GA. Zimmer, M. Wakefield, MD. Silverman, DH. Witzig, TE. Grillo-Lopez, AJ. White, CA. (2000). "Clinical experience with preparation of Zevalin (Ibritumomab Truxetan, IDEC-Y2B(/IDEC-IN2B8) using a radiolabelling kit." Eur J Nucl Med **27:1163 (abstr)**.

Cochran, K. W., J. Doull, et al. (1950). "Acute toxicity of zirconium, columbium, strontium, lanthanum, cesium, tantalum and yttrium." Arch Ind Hyg Occup Med **1**(6): 637-50.

Cremonesi, M., M. Ferrari, et al. (1999). "Three-step radioimmunotherapy with yttrium-90 biotin: dosimetry and pharmacokinetics in cancer patients." Eur J Nucl Med **26**(2): 110-20.

Delongeas, J. L., D. Burnel, et al. (1983). "[Toxicity and pharmacokinetics of zirconium oxychloride in mice and rats]." J Pharmacol **14**(4): 437-47.

DeNardo, G. L., R. T. O'Donnell, et al. (2000). "Radiation dosimetry for 90Y-2IT-BAD-Lym-1 extrapolated from pharmacokinetics using 111In-2IT-BAD-Lym-1 in patients with non-Hodgkin's lymphoma." J Nucl Med **41**(5): 952-8.

Deuber, R. and T. Heim (1991). "Yttrium." Met Their Compd Environ: 1299-308.

DeVita (2001). Cancer principle and practice of oncology, Lippincott Williams & Wilkins.

Durbin, P. W. (1960). "Metabolic characteristics within a chemical family." Health Phys **2**: 225-38.

EMEA website (2004). "Scientific discussion; European Public Assessment Report for Zevalin (Ibritumomab Tiuxetan)." http://www.emea.eu.int/humandocs/Humans/EPAR/zevalin/zevalin.htm.

EU Council (23 March 1998). "1999/575/EC: Council Decision of 23 March 1998 concerning the conclusion by the Community of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes." Official Journal **L 222**(24/08/1999): 0029 - 0030.

EU Council (2001). "Directive 2001/83/EC of the European parliament and of the council of 6 November 2001 on the community code relating to medicinal products for human use." Official Journal **L 311**(28/11/2001): P. 0067 - 0128.

EU Council (2003). "Directive 2003/65/EC of the European Parliament and of the Council of 22 July 2003 amending Council Directive 86/609/EEC on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes." Official Journal **L 230**(16/09/2003): 0032 - 0033.

Frost J.J. and Wagner H.N. (1990). "Quantitative imaging: neuroreceptors, neurotransmitters, amd enzymes." New York: Raven Press.

Gansow, O. A. (1991). "Newer approaches to the radiolabeling of monoclonal antibodies by use of metal chelates." Int J Rad Appl Instrum B **18**(4): 369-81.

Goddu, S. M., R. W. Howell, et al. (1998). "Biological dosimetry of bone marrow for incorporated yttrium-90." J Nucl Med **39**(3): 547-52.
Graca, J. G., F. C. Davison, et al. (1962). "Comparative toxicity of stable rare earth compounds. II. Effect of citrate and edetate complexing on acute toxicity in mice and guinea pigs." Arch Environ Health **5**: 437-44.
Griffiths, G. L., S. V. Govindan, et al. (2003). "90Y-DOTA-hLL2: an agent for radioimmunotherapy of non-Hodgkin's lymphoma." J Nucl Med **44**(1): 77-84.
Haley, T. J. (1965). "Pharmacology and toxicology of the rare earth elements." J Pharm Sci **54**(5): 663-70.
Hartwig, Q. L., T. P. Leffingwell, et al. (1958). "Some toxic effects of yttrium and lanthanum; toxicological studies with yttrium and lanthanum nitrate as modified by site of infection and whole-body radiation." AMA Arch Ind Health **18**(6): 505-10.
Herpst, J. M., J. L. Klein, et al. (1995). "Survival of patients with resistant Hodgkin's disease after polyclonal yttrium 90-labeled antiferritin treatment." J Clin Oncol **13**(9): 2394-400.
Hirano, S., N. Kodama, et al. (1990). "Distribution, localization, and pulmonary effects of yttrium chloride following intratracheal instillation into the rat." Toxicol Appl Pharmacol **104**(2): 301-11.
Hirano, S., N. Kodama, et al. (1993). "Metabolism and toxicity of intravenously injected yttrium chloride in rats." Toxicol Appl Pharmacol **121**(2): 224-32.
Hirano, S. and K. T. Suzuki (1996). "Exposure, metabolism, and toxicity of rare earths and related compounds." Environ Health Perspect **104 Suppl 1**: 85-95.
Hnatowich, D. J., G. Mardirossian, et al. (1991). "Intraperitoneal therapy of ovarian cancer with 90-Yttrium labelled monoclonal antibodies - Preliminary observations." Antibody Immunoconjugates and radiopharmaceuticals **4**(N3): 359-371.
Horovitz, C. T. (2000). "Biochemistry of Scandium and Yttrium." Biochem Elem **13B**.
Johnson, T. K., W. Cole, et al. (2002). "Biokinetics of yttrium-90--labeled huBrE-3 monoclonal antibody." Cancer **94**(4 Suppl): 1240-8.
Jowsey, J., M. Owen, et al. (1955). "Retention and excretion of 90Sr by adult rabbits." Br J Exp Pathol **36**(1): 22-6.
Jowsey, J., H. A. Sisson, et al. (1956). "The site of deposit of Y91 in the bones of rabbits and dogs." J. Nuc;ear Energy **2**: 168-176.
Kahn, D., J. C. Austin, et al. (1999). "A phase II study of [90Y] yttrium-capromab pendetide in the treatment of men with prostate cancer recurrence following radical prostatectomy." Cancer Biother Radiopharm **14**(2): 99-111.
Kidman, B., M. Tutt, et al. (1950). "The retention and excretion of radioactive strontium and yttrium (Sr89, Sr90 and Y 90) in the healthy rabbit." J Pathol Bacteriol **62**(2): 209-27.
Kidman, B., M. L. Tutt, et al. (1951). "The retention of radioactive strontium and yttrium (Sr89, Sr90 and Y90) in pregnant and lactating rabbits and their offspring." J Pathol Bacteriol **63**(2): 253-68.
Knox, S. J., M. L. Goris, et al. (2000). "Phase II trial of yttrium-90-DOTA-biotin pretargeted by NR-LU-10 antibody/streptavidin in patients with metastatic colon cancer." Clin Cancer Res **6**(2): 406-14.
Kutzner, J., A. Eckmann, et al. (1985). "[Blood picture changes in rats after 90Y-citrate administration]." Nuklearmedizin **24**(2): 87-9.
Kyker, G. C. and E. A. Cress (1957). "Acute toxicity of yttrium, lanthanum, and other rare earths." AMA Arch Ind Health **16**(6): 475-9.
Lambert, C. E. (1994). "Acute toxicology evaluation of Yttrium nitrate." Journal of America College of Toxicology **12/6**(6): 629.
Lambert, C. E. (1994). "Acute toxicology evaluation of Yttrium oxide." Journal of America College of Toxicology **12/6**(6): 630.
Lassen, N. and S. Holm (1992). "Single photon emission computed tomography (SPECT)." In: Mazziotta, J. C., Gilman, S. Clinical brain imaging: principles and applications. **108**.
Leimer, M., A. Kurtaran, et al. (1998). "Response to treatment with yttrium 90-DOTA-lanreotide of a patient with metastatic gastrinoma." J Nucl Med **39**(12): 2090-4.
Lenarczyk, M., S. M. Goddu, et al. (2001). "Biologic dosimetry of bone marrow: induction of micronuclei in reticulocytes after exposure to 32P and 90Y." J Nucl Med **42**(1): 162-9.

Linden, O., J. Tennvall, et al. (2001). "Durable response to 90Y-Epratuzumab (hLL20 in B-cell lymphoma failing chemotherapy by using dose-fractionation schedule." Blood **73**(11 Part 1): 602a.

Lloyd, D. C. and E. J. Reeder (1978). "Chromosome aberrations and intra-articular yttrium-90." Lancet **1**(8064): 617.

Luckey, T. D. and B. Venugopal (1978). "Yttrium in : Metal Toxicity in Mammals." Physiological and Chemical Basis of Metal Toxicity **1**: 131-135.

Mazziotta, J. C. and S. Gilman (1992). "Clinical brain imaging: principles and applications." **108**.

McFee, A. F., S. D. Robertson, et al. (1994). "Cytogenetic damage in marrow cells of mice after injections of yttrium-90-labeled monoclonal antibody." Nucl Med Biol **21**(8): 1109-14.

Mill, A. J., J. Wells, et al. (1996). "Micronucleus induction in human lymphocytes: comparative effects of X rays, alpha particles, beta particles and neutrons and implications for biological dosimetry." Radiat Res **145**(5): 575-85.

Mu C.J. and Shi W.L. (1985). "The investigation of mutagenicity and teratogenicity from rare earth compounds New Frontiers in Rare Earth Science and Applications." Science Press **2**: 1530-1534.

Nakamura, Y., Y. Tsumura, et al. (1993). "Studies on the biological effects of Rare Earth Elements: V. Relationship between the concentration of Rare Earth Elements and 9 minerals in various organs in the rat after intravenous administration of Dysprosium, Europium, Ytterbium and Yttrium by low or high dose." Japanese Journal of Toxicology and Environmental Health **39**(2): 121-131.

Nakamura, Y., Y. Tsumura, et al. (1997). "Differences in behavious among the chlorides of seven Rare Earth Elements administered intravenously to rats." Fundamental and applied Toxicology **37**(2): 106-116.

Nakamura, Y., Y. Tsumura-Hasegawa, et al. (1991). "Studies on the biological effects of Rare Earth Elements: Fate of chlorides of Dy, Eu, Yb and Y in the rat after intravenous administration." Eisei Kagaku **37**(6): 497-506.

Nakamura, Y., Y. Tsumura-Hasegawa, et al. (1991). "Studies on the biological effects of Rare Earth Elements: II. Distribution and the histological effects of Dy, Eu, Yb and Y in the rat after intravenous administration." Eisei Kagaku **37**(6): 489-496.

Ogawa, Y., S. Suzuki, et al. (1992). "Twenty-eight-day repeated dose toxicity test of Europium and Gadolinium in Wistar rat in comparison with lanthanum and Yttrium." Journal of the Tokyo Dental College Society **80**(9): 1303-1307.

Otte, A., R. Herrmann, et al. (1999). "Yttrium-90 DOTATOC: first clinical results." Eur J Nucl Med **26**(11): 1439-47.

Paganelli, G., C. Grana, et al. (1999). "Antibody-guided three-step therapy for high grade glioma with yttrium-90 biotin." Eur J Nucl Med **26**(4): 348-57.

Pavelka, K., W. Meier-Ruge, et al. (1975). "Histological study of effects of colloidal 90 yttrium on knee joint tissues of rabbits." Ann Rheum Dis **34**(1): 64-9.

Ramsden, E. N. (1961). "A review of experimental work on radioytrium comprising. I. The tissue distribution. 2. The mechanism of deposition in bone. 3. The state in the blood." Int J Radiat Biol **3**: 399-410.

Rosenblum, M. G., J. J. Kavanagh, et al. (1991). "Clinical pharmacology, metabolism, and tissue distribution of 90Y-labeled monoclonal antibody B72.3 after intraperitoneal administration." J Natl Cancer Inst **83**(22): 1629-36.

Schumacher, T., S. Hofer, et al. (2002). "Local injection of the 90Y-labelled peptidic vector DOTATOC to control gliomas of WHO grades II and III: an extended pilot study." Eur J Nucl Med Mol Imaging **29**(4): 486-93.

Sharkey, R. M., A. Brenner, et al. (2003). "Radioimmunotherapy of non-Hodgkin's lymphoma with 90Y-DOTA humanized anti-CD22 IgG (90Y-Epratuzumab): do tumor targeting and dosimetry predict therapeutic response?" J Nucl Med **44**(12): 2000-18.

Stevenson, A. F., R. Daculsi, et al. (1982). "Haematological studies on 90Sr-90Y-toxicity: II. Femoral CFU-s kinetics and mitogen response of spleen cells." Radiat Environ Biophys **20**(4): 275-87.

Stewart, J. S., V. Hird, et al. (1990). "Intraperitoneal yttrium-90-labeled monoclonal antibody in ovarian cancer." J Clin Oncol **8**(12): 1941-50.

Thomassen, P. R. and H. M. Leicester (1964). "Uptake of Radioactive Beryllium, Vanadium, Selenium, Cerium, and Yttrium in the Tissues and Teeth of Rats." J Dent Res **43**: 346-52.
Valkema, R., M. De Jong, et al. (2002). "Phase I study of peptide receptor radionuclide therapy with [In-DTPA]octreotide: the Rotterdam experience." Semin Nucl Med **32**(2): 110-22.
Vriesendorp, H. M., J. M. Herpst, et al. (1991). "Phase I-II studies of yttrium-labeled antiferritin treatment for end-stage Hodgkin's disease, including Radiation Therapy Oncology Group 87-01." J Clin Oncol **9**(6): 918-28.
Waldherr, C., M. Pless, et al. (2002). "Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq (90)Y-DOTATOC." J Nucl Med **43**(5): 610-6.
Waldmann, T. A., J. D. White, et al. (1995). "Radioimmunotherapy of interleukin-2R alpha-expressing adult T-cell leukemia with Yttrium-90-labeled anti-Tac." Blood **86**(11): 4063-75.
Watanabe, N., N. Oriuchi, et al. (1999). "Effect of edetate calcium disodium on yttrium-90 activity in bone of mice." Ann Nucl Med **13**(6): 397-400.
Weiden, P. L., H. B. Breitz, et al. (2000). "Pretargeted radioimmunotherapy (PRIT) for treatment of non-Hodgkin's lymphoma (NHL): initial phase I/II study results." Cancer Biother Radiopharm **15**(1): 15-29.
Wiseman, G. A., L. I. Gordon, et al. (2002). "Ibritumomab tiuxetan radioimmunotherapy for patients with relapsed or refractory non-Hodgkin lymphoma and mild thrombocytopenia: a phase II multicenter trial." Blood **99**(12): 4336-42.
Wiseman, G. A., B. R. Leigh, et al. (2003). "Additional radiation absorbed dose estimates for Zevalin radioimmunotherapy." Cancer Biother Radiopharm **18**(2): 253-8.
Witzig, T. E., L. I. Gordon, et al. (2002). "Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma." J Clin Oncol **20**(10): 2453-63.
Wong, J. Y. C., D. Z. Chu, et al. (2000). "A phase I radioimmunotherapy trial evaluating 90yttrium-labeled anti-carcinoembryonic antigen (CEA) chimeric T84.66 in patients with metastatic CEA-producing malignancies." Clin Cancer Res **6**(10): 3855-63.