YMM-1

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Yttrium (^{90}Y) citrate CIS bio international, 150-370 MBq/mL at calibration date, suspension for intraarticular injection.
Reference : YMM-1

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Yttrium (^{90}Y) citrate : 150-370 MBq/mL at the date and time of calibration.

Yttrium (^{90}Y) is a pure beta radiation emitter (maximum beta energy = 2.28 MeV).

The half-life is 64 hours. The stable daughter is zirconium.

Excipient with known effect: sodium
Yttrium (^{90}Y) citrate CIS bio international contains 7.4 mg/mL of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for intraarticular injection.

Milky white colloidal suspension with a pH between 5.5 and 7.5, and a non filterable fraction of total radioactivity at least equal to 85% at release date and at least equal to 80% at expiry date. The colloid fraction is composed of particles with a median size of between 3 µm and 6 µm (Laser Diffraction Technique).

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Therapeutic irradiation of synovial hypertrophy of the knee joints (isotopic radiation synovectomy) mainly for mono- or oligo- arthritis of chronic inflammatory rheumatism particularly rheumatoid arthritis.

Yttrium (^{90}Y) citrate CIS bio international is indicated in adults.

4.2. Posology and method of administration

Posology

The usual injected activity ranges from 185 to 220 MBq per joint. Several radiation synovectomies can be performed simultaneously or successively.
Reinjection of radioactive colloid in one articulation can be performed after a period of 6 months in the event of relapse. The recommended activity range for re-treatment is 110-220 MBq. Two failed injections should not be followed by subsequent radiation synovectomy treatments. The annual activity for treatment of one joint should not exceed 440 MBq.

Method of administration

Intraarticular use.

The product is ready to use and should not be diluted prior to administration.

Multidose.

The recommended injection procedure is as follows:

- Evacuation of any articular effusion
- Intraarticular injection of the yttrium-90 colloid suspension
- Injection by the same route of a cortisone derivative (e.g. prednisolone acetate 25 mg or hydrocortisone acetate 50 mg).
- Rinsing of the needle before withdrawal either with saline solution or with corticosteroid solution to avoid reflux and cutaneous radionecrosis.

The injection procedure must be followed by immobilisation of the knee with bed rest for 2 or 3 days to reduce extra articular migration of the radiopharmaceutical (see section 4.4).

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- In pregnancy or breastfeeding.
- In localised infections or skin disorders present in the injection area.
- In septic arthritis.
- In ruptured popliteal cysts.

4.4. Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.

The injectable suspension is only designed for intraarticular injection and must not be injected intravenously or into the urinary bladder.

After the procedure
The injection procedure must be followed by immobilisation of the knee with bed rest for 2 or 3 days to reduce extra articular migration of the radiopharmaceutical (see section 4.2).

In women still in reproductive age, effective contraception must be continued for several months after treatment (see section 4.6).

Specific warnings

Patients still in reproductive age
In case of any use before conclusion of the reproductive phase the potential benefits and possible adverse events must be carefully considered and balanced.

If there is a popliteal cyst in danger of rupturing suitable diagnostic measures (e.g. sonography) should be applied to rule out this possibility.

Application is only to take place in exceptional circumstances, and then with the utmost care, when there are seriously unstable knee joints, clear destruction of bone tissue or stiffened articulations.
Care is also to be taken in cases of significant cartilage loss within the joint.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

Precautions with respect to environmental hazard are in Section 6.6.

4.5. Interaction with other medicinal products and other forms of interaction

Yttrium (^{90}Y) may be released from the yttrium citrate colloid after local interaction with X-ray contrast media that contain EDTA or other chelating agents.

In the case of contrast media containing EDTA or other chelating agents, the risk of a relevant interaction with yttrium (^{90}Y) is determined above all by the elimination rate of the contrast medium. Ionic high-osmolar and nonionic low-osmolar monomeric contrast media are both eliminated from a healthy joint with a half-life period of between 30 and 60 minutes. This time may be even shorter in the case of rheumatic joints. The observance of a wide safety margin of 8 hours is nevertheless recommended between the administration of the X-ray contrast medium and yttrium (^{90}Y) citrate, in order to eliminate the risk of interaction. Given the slow elimination rate of dimeric non-ionic contrast media containing EDTA or other chelating agents, a safety margin of 3 days should be observed.

4.6. Fertility, pregnancy and lactation

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

Contraception in females
If isotopic radiation synovectomy however proves indispensable in a woman of childbearing age, prior effective contraception is imperative, and should be continued several months after treatment.

Pregnancy
The use of yttrium (^{90}Y) citrate is contraindicated in pregnant women due to the potential risk of leakage from the joint (see section 4.3).

Breastfeeding
The use of yttrium (^{90}Y) citrate is contraindicated in beastfeeding mother (see section 4.3).

Before administering radiopharmaceuticals to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding.

4.7. Effects on ability to drive and use machines

Not relevant.

4.8. Undesirable effects

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

The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases it is necessary to ensure that the risks of the radiation are less than the disease itself. The effective dose is 8.4 mSv when the maximal recommended activity of 220 MBq is administered.

Secondary effects

The following table presents how the frequencies are reflected in this section:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

In the following table the undesirable effects are classified in accordance with the MedDRA SOCs.

Tabulated summary of adverse reactions
Tabulated list of adverse reactions ordered according to MedDRA (Medical Dictionary for Regulatory Activities) system organ classes (SOCs) with their frequency stated

MedDRA Body system SOCs	**Preferred term**	**Frequency**
Infections and infestations	Arthritis infective	Very rare
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Myeloid leukaemia	Very rare
	Lymphoma	Very rare
Immune system disorders	Hypersensitivity	Uncommon
Skin and subcutaneous tissue disorders	Skin necrosis	Uncommon
	Pigmentation disorders	Uncommon
Musculoskeletal and connective tissue disorders	Osteonecrosis	Not known
Congenital, familial and genetic disorders	Cytogenetic abnormality	Very rare
General disorders and administration site conditions	Pyrexia	Common
	Pain	Uncommon
	Inflammation	Uncommon

Description of adverse reactions:

A transient fever reaction may be observed within 24 hours of radiation synovectomy in about 2 % of the cases.

In some cases, allergic reactions have been observed.

Radioactive colloid injection may be painful in some cases.

Inflammatory flare-up at the joint may occur several hours or days after radiation synovectomy. This can be treated by analgesics and non-steroid anti-inflammatory drugs.

Cutaneous necrosis or blackish dermal-epidermal pigmentation is unusual after radiation synovectomy. This adverse reaction may arise after reflux of the product via the needle, or if injection is too close to an articular breach due to synovial biopsy or to arthroscopy.

Secondary arthritis infective after radiation synovectomy is exceptional.

Cases of knee osteonecrosis have been reported.

Side effects due to radiation exposure

After radiation synovectomy of the knee with Yttrium (^{90}Y) colloid suspension for local injection, cytogenetic abnormality are seen in the lymphocytes in the same proportions as in hyperthyroid patients treated with iodine 131. The mean yield of dicentrics - centrics rings per 37 MBq per 100 cells was reported to be less than 0.57.

The frequency of chromosome aberrations serves as a quantitative indicator for cell damage and correlates, under certain conditions, to the dose applied. Special investigations of chromosome aberrations in peripheral lymphocytes have however not revealed any significant increase in the quantity of dicentric chromosomes (radiation-related chromosome aberrations) as a result of isotopic radiation synovectomy with Yttrium (^{90}Y) citrate.

Only a single case of chronic myelogeneous leukaemia and only a single case of malignant inguinal lymphoma occurred after the treatment of more than 20,000 joints throughout a maximum follow up period of twenty years. However the relationship of these pathologies to radiation synovectomy was not ascertained.

4.9. Overdose

As the use of Yttrium (^{90}Y) citrate is restricted to appropriately-trained medical professionals, the likelihood of an overdose occuring is very low. If an overdose should occur however, the same treatment as normally used for radiogenic synovitis should be applied. Given the low rate of elimination of radionuclide from the body, the specified dose cannot be reduced. The joint is immobilised and cooled if necessary. If an effusion forms, it should only be punctured if the clinical symptoms make this course of action necessary. The intra-articular injection of a corticoid is only required in case where symptoms are otherwise difficult to treat. Extra-articular accumulation of beta emitter can lead to necrosis, which must be treated immediately by injecting corticoids around the affected area.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group : Therapeutic Radiopharmaceuticals: Anti-inflammatory agents: Yttrium (^{90}Y) compounds: Yttrium (^{90}Y) citrate colloid

ATC code : V10AA01

Mechanism of action
Yttrium-90 is a radionuclide with a 64 hours half-life, which emits β^- radiation with maximum energy of 2.28 MeV with mean pathway of 3.6 mm in the soft tissues (maximum 11 mm); mean pathway in the cartilage is 2.8 mm (maximum 8.5 mm).

After intraarticular injection, radioactive colloids are phagocytosed by the superficial synovial cells. Due to irradiation, necrosis of the superficial synovial layer is observed from the first day on. After a period of several months, synovial fibrosis is apparent with a decreaseof inflammatory infiltrates, of the size and number of synovial folds, and of thickness of the neighbouring layer. Nevertheless, areas of synovitis may persist, leading to the reconstitution of a neo-synovial membrane, with or without persistent attenuated synovitis. This histological evolution occurs parallel with the gradual resolution of clinical signs of articular inflammation.

The mechanism of action of the radiocolloid on the malignant effusions is not well understood.

Clinical efficacy
The efficacy of these substances may be due to their lethal effect on free floating malignant cells. It has also been suggested that their beneficial effects may result from the irradiation of malignant serosal surface seedings or from a specific radiation effect upon mesothelial surfaces.

5.2. Pharmacokinetic properties

Distribution:
The product is administered as a single intraarticular dose for radiation synovectomy. The distribution and diffusion of the radionuclide from its site of action were studied in the rabbit: after injection of 0.59 MBq of Yttrium-88 (isotope chosen for its gamma radiation, which increases counting precision), a study reported that 87 to 100 % of the injected yttrium was recovered in the articulation after 7 days. The autoradiography showed uniform distribution in the synovial membrane. In experimental arthritis, 40 minutes after intraarticular injection of 0.37 MBq of Yttrium-90, 25 % of the administered activity was recovered in the synovial fluid.

Possible leakage from the joint into the regional lymph nodes, and thus the possibility of exposure to radiation of the lymphocytes and the liver, may depend on the movement of the joint. Therefore, immobilization of the treated joint is recommended for the duration of one physical half-life of Yttrium-90 (~3 days).

Elimination:
A study in the rabbit showed that, 24 hours after intraarticular injection of 3.7 MBq to 37 MBq of Yttrium-90, 0.2 % of the activity was recovered in the blood, and 0.4 % and 0.13 % in urine and faeces respectively

5.3. Preclinical safety data

Toxicological studies with rats have demonstrated that with a single IV injection of yttrium chloride at a dose of 3 to 5 mg/kg of yttrium (5 to 8 times the total amount of injected yttrium in patients) no death were observed.

Toxicity with repeated administration of 0.03 mg/kg/day over 28 days in rats was not observed.
This agent is not intended for regular or continuous administration.

Mutagenicity studies and long term carcinogenicity studies have not been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride
Water for injections
Sodium hydroxide (for pH adjustment)
Nitric acid
Sodium citrate

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3. Shelf Life

15 days from the date of manufacture.
The expiry date is indicated on the outer packaging and on each vial.

8 hours after first withdrawal.

After the first withdrawal, store in a refrigerator (2°C-8°C).

6.4. Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original packaging.

For storage conditions after first withdrawal of the medicinal product, see section 6.3.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5. Nature and contents of container

15 ml, type I Ph.Eur., clear colorless glass vial containing a colloidal milky white sterile suspension, closed with chlorobutyl rubber stoppers and aluminium capsules. The sealed, capped vial is placed in a protective lead container. The entire assembly is then placed in a metal box fitted with polystyrene supports for shipping.

Pack size: 1 multidose vial containing 0.5 to 10 mL.

6.6. Special precautions for disposal and other handling

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

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

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

Product ready to use.

Usual precautions regarding sterility and radioprotection should be respected.

The packaging, the pH and the activity must be checked before use.

The vial should never be opened and must be kept inside its lead shielding when being used. The product should be aseptically withdrawn through the stopper using sterilized single use needle and syringe after disinfection of the stopper.

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

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

7. MARKETING AUTHORISATION HOLDER

CIS bio international
RN 306 - Saclay
B.P. 32 - 91192 GIF-SUR-YVETTE CEDEX
FRANCE

8. MARKETING AUTHORISATION NUMBER

Country specific

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Country specific

10. DATE OF REVISION OF THE TEXT

03/2013

11. DOSIMETRY

Radiation exposure can be estimated with the aid of the dosimetry table shown below. The estimated radiation exposure values were determined in human subjects or based on model calculation (MIRD/ICRP 60, Monte Carlo simulation).

The data listed in the table below are calculated according to the following assumptions :
It is assumed that the leakage of colloidal radiopharmaceutical out of the knee occurs with the lymph, that the colloid is first transported to the inguinal lymph nodes, and that it passes via further lymph nodes into the circulation. It is then quickly taken up by the reticuloendothelial system.

The results marked with an asterisk (*) were determined using MIRDOSE 3.1 on the basis of uptake of radiation dose by organs estimated on the most unfavourable case, i.e. using residence time [(fraction in organ x half-life/ln2) x leakage fraction] for small colloids (<100 nm particles). The median activity leakage value of 1.8% is taken as a basis for estimating radiation exposure due to leakage activity.

For the particularly sensitive gonads, dose of radiation absorbed was determined by using MIRDOSE 3.1 and by adding measured values of bremsstrahlung from the treated knee and regional lymph nodes.

Table 1: The dose of radiation absorbed by organs (mGy/MBq injected) and the effective dose (mSv/MBq injected) after injection into the knee joint

Exposure to radiation (mGy/MBq) after intra-articular injection into the knee joint	
Organ/Part of the body	**Dose absorbed per activity administred (mGy/MBq)** **Adults**
Synovia	700
Regional lymph nodes: with low rate of leakage with higher rate of leakage	 3.1 8.2
Testes	0.0022
Ovary	0.0019
Liver	0.328*
Spleen	0.489*
Kidneys	0.000634*
Bone surface (whole body)	0.0336*
Red bone marrow	0.0528*
Whole body	0.0121*
Effective dose	0.0380 mSv/MBq

The effective dose resulting from intra-articular administration of an activity of 220 MBq is approximately 8.4 mSv for a subject of 70 kg.

Radiation dose to specific organs, which may not be the target articulation (into the knee joint) of therapy, can be influenced significantly by pathophysiological changes induced by the disease process. This should be taken into consideration when using the following information.

For an administered activity of 220 MBq the typical radiation dose to the target knee joint is 154 Gy and the typical radiation doses to the critical organs are: Testes: 0.48 mGy; Ovary: 0.42 mGy; Regional lymph nodes with low leakage: 682 mGy; Regional lymph nodes with high rate of leakage: 1804 mGy; Liver: 72.2 mGy; Spleen: 107.6 mGy; Kidneys: 0.14 mGy.