SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Yttrium $^{90}$Y colloidal CIS bio international, suspension for local injection
Reference : YMM-1

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Yttrium $^{90}$Y citrate : 37-370 MBq/mL at calibration date
Contains no antimicrobial preservative
Yttrium $^{90}$Y is a pure beta radiation emitter (maximum beta energy = 2.25 Mev).
The half life is 64 hours. The stable daughter is zirconium.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Suspension for injection.

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.
4.2. **Posology and method of administration**

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

**Posology**

*Intraarticular administration*:

The usual injected activity ranges from 111 to 222 MBq per joint. Several radiation synovectomies can be performed simultaneously or successively. Re-injection of radioactive colloid in one articulation can be performed after a period of 6 months in the event of relapse.

**Method of administration**

*Intraarticular administration*:

If there is a popliteal cyst, knee arthrography should be done at least 8 days before the injection to localise the cyst in order to avoid its rupture that would bring about a communication between the cyst and the articular cavity.

The recommended injection procedure is as follows:

- Evacuation of any articular effusion
- Strictly 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 knee with bed rest for 2 or 3 days to reduce extra articular migration of the radiopharmaceutical.

4.3. **Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- In pregnant women.
- In septic arthrisis and in synovial cyst rupture.

As far as possible, this compound should be avoided in children during bone growth and in young subjects with reproductive potential.

In patients with unstable knee joint, severe destruction and sequestration, yttrium \[^{90}\text{Y}\]\ colloid may be justified in special circumstances although caution is advised.
4.4. **Special warnings and precautions for use**

Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorisation for the use and manipulation of radionuclides.

This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations.

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

A delay of at least 8 days has been recommended after local use of contrast media as these normally contain EDTA or other chelating agents which may remove yttrium from the colloid media.

4.6. **Pregnancy and lactation**

Pregnancy contraindicates injection of yttrium $^{90}$Y because of the potential risk of leakage from the joint.

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

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

Before administering a radioactive medicinal product to a mother who is breast feeding consideration should be given as to whether the therapy could be reasonably delayed until the mother has ceased breast feeding.

4.7. **Effects on ability to drive and use machines**

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

4.8. **Undesirable effects**

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended therapeutic result.

Exposure to ionising radiation is linked with cancer induction and 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.
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 articular infection after radiation synovectomy is exceptional.

After radiation synovectomy of the knee with yttrium [\(^{90}\)Y], chromosomal aberrations 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 (1 mCi) per 100 cells was reported to be less than 0.57.

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.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Statens legemiddelverk
Nettstid: [www.legemiddelverket.no/meldeskjema](http://www.legemiddelverket.no/meldeskjema)

4.9. **Overdose**

In the event of the administration of a radiation overdose, the absorbed dose can not be reduced due to poor elimination of the radionuclide from the body.

5. **PHARMACOLOGICAL PROPERTIES**

5.1. **Pharmacodynamic properties**

Pharmacotherapeutic group: Radiopharmaceuticals for therapeutic use: Anti-inflammatory agents.
ATC code: V 10 AA 01.

Yttrium [\(^{90}\)Y] is a radionuclide with a 2.7 day half-life, which emits \(\beta^-\) radiation with maximum energy of 2.2 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 intra-articular 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 decrease of 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 to the gradual resolution of clinical signs of articular inflammation.

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

The product is administered as a single intra-articular dose for radiation synovectomy. The distribution and diffusion of the radioelement from its site of action were studied in the rabbit:

After injection of 0.59 MBq (16 μCi) of yttrium-88 (isotope chosen for its gamma radiation, which increases counting precision), a study reported that 87 to 100 % of the injected yttrium is recovered in the articulation after 7 days. Another study showed that 24 hours after intraarticular injection of 3.7 MBq to 37 MBq of yttrium-90, 0.2 % of the activity is recovered in the blood, and, 0.4 and 0.13 % in urine and faeces, respectively.

The autoradiography showed uniform distribution in the synovial membrane. In experimental arthritis, 40 minutes after intra-articular injection of 0.37 MBq of yttrium-90, 25 % of the administered activity was recovered in the synovial fluid.

5.3. Preclinical safety data

No available data.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride
Water for injections
Sodium hydroxide

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf-life

15 days from the date of manufacture.

The expiry date is indicated on the outer packaging and on each vial.

24 hours after first withdrawal.
6.4. **Special precautions for storage**

Do not store above 25°C. Store in the original package.

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

6.5. **Nature and contents of container**

15 mL, colourless, European Pharmacopoeia type I drawn glass, closed with chlorobutyl rubber stoppers and aluminium capsules.

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

6.6. **Special precautions for disposal and other handling**

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

7. **MARKETING AUTHORISATION HOLDER**

CIS bio international
BP 32
91192 GIF-SUR-YVETTE CEDEX
FRANCE

8. **MARKETING AUTHORISATION NUMBER**

MTnr 8312

9. **DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**

First authorisation: 08-10-1998
Renewal of authorisation: 31-01-2010

10. **DATE OF REVISION OF TEXT**

2015-12
11. **DOSIMETRY**

The half-life is 64 hours. The stable daughter is zirconium. The level of gamma impurities is less than 1 %.

For administered activity of 222 MBq (6 mCi) of yttrium-90 injected into the knee joint, for a 150 cm² synovial area, an absorbed dose of 50 Gy is obtained at a depth of 2.5 mm.

Beyond the synovial tissue, which constitutes the target organ, the regional lymph nodes received the highest irradiation. This has been considerably reduced and brought down to an acceptable level by prescribing bed rest systematically for 2 or 3 days, to reduce extra-articular migration of the radiopharmaceutical and thus reduce its uptake by the lymph nodes. Hence, mean irradiation for the inguinal lymph nodes after knee radiation synovectomy with 222 MBq (6 mCi) yttrium-90, amounts to 2 Gy with bed rest.

Administered activity of 185 MBq (5 mCi) of yttrium-90 injected in the knee delivers radiation of about 0.13 Gy to the whole body, and 0.05 Gy to the liver.

In radiation synovectomy of the knee with yttrium-90, the dose absorbed by the gonads is 1.1 μGy/MBq.

No other dosimetric data are currently available.

12. **INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS**

Yttrium [⁹⁰Y] colloid CIS bio international is a sterile suspension of colloidal yttrium-90 with a pH between 5.5 and 7.5, a non filterable fraction of total radioactivity at least equal to 85% at release date and at least equal to 80% at expiry date. And with a radioactive concentration in the range of 37-370 MBq/mL at the date stated on the label (calibration date).

Yttrium [⁹⁰Y] citrate CIS bio international is presented as colloid suspension in which 50 % of the particles have an average diameter from 3 µm to 6 µm (Laser diffraction technique).

Usual precautions regarding sterility and radioprotection should be respected.

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 sterilised single use needle and syringe after desinfection of the stopper.

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

Detailed information on this medicinal product is available on the website of NoMA.