IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0677/013/001
Case No: 2056589

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

CIS bio international

BP 32, **91192 Gif-Sur-Yvette Cedex**, **France**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Yttrium (^{90}Y) Colloid CIS bio international, colloid suspension for local injection.
Reference: YMM-1

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **19/03/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Yttrium (^{90}Y) Colloid CIS bio international, colloid suspension for local injection.
Reference: YMM-1

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Yttrium (^{90}Y) Citrate : 37-370 MBq/ml at calibration date

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 local injection.
Clear and colourless suspension.

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.

4.2.1 Posology

Intraarticular administration:

The usual injected activity ranges from 111 to 222 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.

4.2.2 Method of administration

Intraarticular administration:

If there is a popliteal cyst, knee arthrography should be done at least 8 days before the injection to localize 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
- 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.

4.3 Contraindications

- hypersensitivity to the active substance or to any excipients
- in pregnant women.
- in septic arthritis 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 joints, severe destruction and sequestration, yttrium (^{90}Y) citrate 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 use of Yttrium (^{90}Y) colloid suspension for local injection 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, and 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, and should be continued several months after treatment.

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

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 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 risk of the radiation is less than the disease itself.

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

In some cases, allergic reactions (hypersensitivity) have been observed.

Radioactive colloid injection may induce pain in some cases. Inflammation at the joint may occur several hours or days after radiation synovectomy. This can be treated by analgesics and non-steroid anti-inflammatory drugs.

Skin necrosis or pigmentation disorder 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 infective arthritis after radiation synovectomy is exceptional.

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.

Only a single case of myeloid leukaemia and only a single case of 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

In the event of the administration of a radiation overdose, the absorbed dose cannot 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 : V10AA01

Yttrium-90 is a radionuclide with a 2.7 day half-life, which emits β^-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 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 onwards. Synovial fibrosis is apparent after a period of several months with decreased inflammatory infiltrates, the size and number of synovial folds, and the 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. 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 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. Another study 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. 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.

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 compatability studies, this medicinal product must not be mixed with other medicinal product.

6.3 Shelf Life

15 days from the date of manufacture.
The expiry date is indicated on the outer packaging and on each vial.
To be used within 24 hours after first withdrawal.

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original packaging.
After the first withdrawal, store in a refrigerator (2^{o} C – 8^{o}C).
The product should be stored in accordance with national regulations for radioactive materials.

6.5 Nature and contents of container

15 ml, type I Ph. Eur., clear, colourless glass vial containing a clear, colourless sterile suspension, closed with chlorobutyl rubber stoppers and aluminium capsules. The sealed, capped vial is place in a protective lead container.

The entire assembly is then placed in a metal box with polystyrene supports for shipping.
Pack size: 1 multidose vial containing 1 to 10 ml.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

PA 677/13/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 March 1999

Date of last renewal: 19 March 2009

10 DATE OF REVISION OF THE TEXT

July 2010

11 DOSIMETRY

For administered activity of 222 MBq of Yttrium-90 injected into the knee joint, for a 150 cm^2 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 radiation. This has been considerably reduced and brought down to an acceptable level by prescribing bed rest 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 of Yttrium-90 amounts to 2 Gy with bed rest.

Administered activity of 185 MBq 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 [^{90}Y] citrate CIS bio international is presented as a 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 sterilized single use needle and syringe after disinfection 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 the Irish Medicines Board.