SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Erbium (^{169}Er) citrate CIS bio international 111 MBq/ml suspension for local injection.
Reference: ERMM-1

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Erbium (^{169}Er) citrate: 111 MBq/ml at the date of calibration

Erbium-169 is a beta-emitter (maximum energies: 343.6 keV, intensity: 42 %, and 352.0 keV, intensity: 58 %) and gamma-emitter of low intensity (energy: 8.4 keV, intensity: 0.2 %). The half-life is 9.40 days. The radioactivity related to the major emitting gamma impurities constitutes a maximum of 0.38 % of the total radioactivity at calibration date.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for local injection.

Colloidal milky white suspension with a median particle size between 3 µm and 6 µm (Laser diffraction technique) and a pH between 5.5 and 7.5.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Erbium (^{169}Er) citrate is indicated in adults for the treatment of rheumatoid mono- or oligo-arthritis involving one or few of the small joints of the hands and feet following failure of intra-articular corticosteroid therapy or when the latter is contra-indicated.

4.2. Posology and method of administration

Posology
The activity to be administered depends on size of the type joint, synovial thickness and the amount of joint effusion. The following activities are recommended:

- 10 to 20 MBq for proximal or distal interphalangeal joints
- 20 to 40 MBq for metacarpophalangeal or metatarsophalangeal joints
- 20 to 80 MBq for trapeziometacarpal joints.

Several synoviortheses may be conducted concomitantly or in succession.

A repeat injection of radioactive colloid into a joint should not be administered until at least six months have elapsed. Two failed injections should not be followed by subsequent treatments.

Method of administration

Multidose vial.
The injection must be strictly intra-articular and conducted under arthrographic guidance.

The recommended procedure is as follows:

- Local anesthesia of the joint using 1 or 2 % xylocaine
- Drainage of any articular effusion
- Intra-articular injection of the erbium-169 colloidal suspension
- Injection, by the same route, of a corticosteroid (e.g. hydrocortisone acetate or prednisolone acetate)
- Before withdrawal of the needle, needle flushing with normal saline or corticosteroid solution to prevent reflux and cutaneous radionecrosis.

Following administration, the treated joint must be immobilized using splints (upper limbs) or bed rest (lower limbs) for at least 48h (see section 4.4).

4.3. Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- pregnancy
- lactation
- children and young patients under 20 years
- septic arthritis.
- localised infections or altered skin conditions present in the injection area
- recently ruptured synovial cyst communicating with articular cavity

4.4. Special warnings and precautions for use

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.

Patient of childbearing potential
In woman of reproductive age, effective contraception must be instituted before administration of the radiopharmaceutical and pursued for several months following treatment discontinuation (see section 4.6).

After the procedure
Following administration, the treated joint must be immobilized in order to restrict extra-articular diffusion of the radiopharmaceutical (see section 4.2).

Specific warnings
The most rigorous asepsis must be ensured during injection. Radiosynoviorthesis is subject to the same risks that apply to any joint-puncturing procedure for the application of intra-articular treatment.

Precautions with respect to environmental hazard see section 6.6.

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

Erbium (^{169}Er) citrate may be released from the erbium 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 erbium (^{169}Er) citrate is determined above all by the elimination rate of the contrast medium. Ionic, high-osmolar and non-ionic 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 eight hours is nevertheless recommended between the application of the X-ray contrast medium and the erbium (^{169}Er) 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 three 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
If synoviorthesis is considered indispensable in woman of reproductive age, effective contraception must be instituted before administration of the radiopharmaceutical and pursued for several months following treatment discontinuation.

Pregnancy
The use of erbium (^{169}Er) citrate is contraindicated in pregnant women due potential extra-articular diffusion of the radiopharmaceutical and radiation exposure to the foetus (see section 4.3).

Breast-feeding
The use of erbium (^{169}Er) citrate is contraindicated in breastfeeding women (see section 4.3).

4.7. Effects on ability to drive and use machines

Driving vehicles or using machines is not recommended due to the immobilisation of the joint after administration.

4.8. Undesirable 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 this table the undesirable effects are classified in accordance with the MedDRA SOCs.

MedDRA Body system SOCs	**Preferred term**	**Frequency**
Infections and infestations	Arthritis infective	Not known
General disorders and administration site Conditions	Pyrexia Pain Inflammation	Common Very common Very common
Musculoskeletal and connective tissue disorders	Arthritis flare up Joint range of motion decreased Joint swelling	Very common Common Not known
Skin and subcutaneous tissue disorders	Skin necrosis Dermatitis bullous Pigmentation disorders Erythema Rash Pruritus	Not known Very rare Common Very rare Not known Not known

Description of selected adverse reactions:
- Resurgence of inflammatory phenomena (arthritis flare up) during the first week post administration in about 40 % of cases.
- Frequent reduction in joint function for 1 month

Other disorders
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary effects. The radiation dose resulting from therapeutic exposure may result in a 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 effective dose (E) is 6.6 mSv when the maximal recommended activity of 80 MBq of erbium (^{169}Er) colloid per joint is administered.

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 radiosynoviorthesis with erbium (^{169}Er) citrate.

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 the national reporting system (country specific).

4.9. Overdose

As the use of erbium (^{169}Er) colloid is restricted to appropriately-trained medical professionals, the likelihood of an overdose occurring 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 immobilized and cooled if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory therapeutic radiopharmaceutical, ATC code: V10AX04.

Mechanism of action
Therapeutic activity is based on the effects of beta radiation on the synovial membrane. The maximum range of the released beta radiation in tissue is approximately 1.0 mm.
The radioactive colloid introduced into the area of the joint is phagocytised by the synovial cells on the surface, leading to surface radiation of the synovial membrane with resulting coagulation necrosis of the surface synoviocytes, followed by rejection of the necrotic tissue and a pronounced inflammatory reaction with demarcation.

Pharmacodynamic effects
After a period of several months, there is fibrosing and sclerosing of the synovia with a decline in growth and subdermal inflammation of the joint. The size and quantity of synovial folds is reduced.

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.

5.2. Pharmacokinetic properties

Distribution
The product is administered as a single intra-articular dose for radiation synovectomy. The colloidal erbium (^{169}Er) citrate is distributed homogeneously throughout the joint and is phagocytised by synovial cells, leading to therapeutic irradiation of the synovia.

Organ uptake
Erbium (^{169}Er) citrate is used in a colloidal preparation. This colloidal fixing encourages phagocytosis and reduces the possibility of leakage into regional lymphatic systems and lymph nodes. The median size of the particles in this product range from 3 µm to 6 µm. Possible leakage from the joint into the regional lymph nodes, and thus the possibility of exposure to radiation of lymphocytes and the liver, depends largely on the movement of the joint. This is why it should be immobilised for 48 hours.

Elimination
Experimental studies have been carried out on animals to investigate the distribution and leakage of erbium (^{169}Er) citrate from the joint. After the intra-articular injection of approximately 5 MBq erbium (^{169}Er) citrate into a rabbit's knee, 87% of the injected radioactivity was still present in the joint 13 days later. The calculated residence time of the radioactivity applied to the knee totaled 268 hours.

5.3. Preclinical safety data

The LD_{50} of erbium citrate administered by the intraperitoneal route is 63 mg/kg in the guinea pig and 122 mg/kg in the mouse.

The mass of erbium citrate corresponding to one therapeutic injection is maximum 13 mg (i.e. 6 mg of erbium).

This product is not intended for continuous or regular administration. Accordingly, no mutagenicity or oncogenicity/carcinogenicity studies have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

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

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

18 days from the date of manufacture.
After the first withdrawal store in a refrigerator (2°C – 8°C) and use within 8 hours.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original packaging.
For storage conditions after first withdrawal, see section 6.3.

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

6.5. Nature and contents of container

15 ml vial of type I colourless glass (European Pharmacopoeia) closed by a rubber stopper and capped with an aluminum cap. The vial is enclosed within a lead shield.

Pack size: 1 multidose vial containing 0,5 to 10 mL (55-1110 MBq at calibration date).

6.6. Special precautions for disposal and other handling

General warning
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 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.

Store the vial in its lead protective shielding.
The product is ready to use and should not be diluted prior to administration.

Before use, check the packaging, pH and activity.

Never open the vial. After disinfecting the stopper, aseptically withdraw the suspension through the stopper using a sterile single use syringe and needle.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

Country specific

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Country specific

10. DATE OF (PARTIAL) REVISION OF THE TEXT

04/12/2013

11. DOSIMETRY

The doses absorbed, estimated at joint level, are reported in the following table :

Joint	Activity injected (MBq)	Dose absorbed (Gy) at joint level*			
		at a synovial depth of 0.1 mm	at a synovial depth of 0.2 mm	at a synovial depth of 0.3 mm	at a synovial depth of 0.4 mm
Proximal and distal interphalangeal joints	10 to 20	910 to 1820	330 to 660	130 to 260	50 to 100
Metacarpophalangeal or metatarsophalangeal joints	20 to 40	1820 to 3640	660 to 1320	260 to 520	100 to 200
Trapeziometacarpal joints	20 to 80	1820 to 7280	660 to 2640	260 to 1040	100 to 400

*: Maximum values in the absence of extra-articular diffusion.

Radiation exposure in the regional lymph nodes varies with the amount of lymphogenic dispersed radioactivity and the number of lymph nodes that accumulate radioactivity. With intra-articular application of 80 MBq erbium (^{169}Er) citrate and an assumed accumulation of 3% in the regional lymph nodes, radiation exposure in the lymph nodes can vary between 45.6 Gy (one accumulating lymph node) and 11.5 Gy (four accumulating lymph nodes).

Radiation exposure can be estimated with the help of the dosimetry table shown below. The estimated radiation-exposure values are based on model calculations (OLINDA/ICRP 53 and 60).

Table 1: The dose of radiation absorbed by the organs (mGy/MBq injected activity/% of leakage) and the effective dose after injection of 80 MBq and with a supposed 10% extra-articular leakage (mSv).

Organ	**mGy/MBq/% leakage**	**Injection of 80 MBq with 10% leakage mGy**
Spleen	0.105	84
Liver	0.0702	56.2
Red bone marrow	0.0156	12.5
Osteogenic cells	0.00717	5.7
Kidneys	0.000131	0.1
Uterus	0.000131	0.1
Testes	0.000131	0.1
Ovaries	0.000131	0.1
Other organs	0.000131	0.1
Whole body	0.00261	2.1
	mSv/MBq/% leakage	**mSv**
Effective dose	0.00820	6.6

Lymph nodes and joints are not part of the calculation of the effective dose.

The effective dose after intra-articular application of 80 MBq is 6.6 mSv with an assumed activity leakage from the joint of 10%.

For an administered activity of 80 MBq the typical radiation dose to the critical organs are: one accumulating lymph node with 3% of uptake: 45,6 Gy, four accumulating lymph nodes with 3% of uptake: 11,5 Gy spleen: 84 mGy and liver: 56 mGy.

If the treated joint is not immobilised, this can lead to radiation exposure of regional lymph nodes and high radiation exposure of the lymphocytes.