SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rhenium (^{186}Re) sulphide CIS bio international 148-370 MBq/mL suspension for intra-articular injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Colloidal rhenium (^{186}Re) sulphide: 148 to 370 MBq/mL (at calibration date)

Rhenium-186 emits beta radiation (maximum energies: 939.4 keV, intensity: 21.5 %, and 1076.6 keV, intensity: 71.6 %) and gamma radiation of low intensity (energy: 137.15 keV, intensity: 9.4 %). The half-life is 3.7 days. Rhenium-186 disintegrates by beta emission (92%) into stable osmium-186 and by electronic capture (8%) into stable tungsten-186.

Rhenium (^{186}Re) sulphide CIS bio international is supplied as a colloidal suspension in which at least 95% of particles have a size greater than 50 nm.

Excipient with known effect: sodium (12.7 mg/mL)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for intra-articular injection
Colloidal suspension of pH between 3,5 and 5,5.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

This medicinal product is indicated for use in adults in the treatment of inflammatory arthritis, such as rheumatoid poly-arthritis and haemophilic arthropathy, when there are inflammatory flare-ups in the shoulder, elbow, wrist, ankle or hip.

In children under the age of 18 years, radiation synoviorthesis should only be used in the treatment of haemophilic haemarthrosis and must be indicated as the last resort.

4.2. Posology and method of administration

Posology
In adults and children, the radioactivity administered must be adjusted based on the type of joint to be treated.

- 70 MBq for shoulder, elbow, wrist and ankle,

- 110 MBq for the hip.

Several synoviortheses may be conducted concomitantly or in succession.

In the event of relapse, an interval of 6 months is required before repeat injection into the same joint.

Two failed injections should not be followed by subsequent synoviorthesis treatment.

Method of administration
The injection must be strictly intra-articular and conducted under arthrographic guidance.

The recommended procedure is as follows:

- Local anaesthesia of the joint using 1 or 2 % xylocaine
- Drainage of any articular effusion
- Intra-articular injection of the rhenium-186 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 an injectable saline solution or corticosteroid solution to prevent reflux and cutaneous radio-necrosis.

Following administration, the joint must be immobilized using splints (upper limbs) or confinement to bed (lower limbs) for 3 days in order to restrict extra-articular diffusion of the radio-pharmaceutical product.

For instructions on preparation of the medicinal product before administration, see section 6.6.

For patient preparation, see section 4.4.

4.3. Contra-indications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- In pregnancy or breast-feeding
- In the event of septic arthritis or sinovial cyst rupture
- In children during the bone growth phase
- In case of simultaneous intra-articular injection in the hip of a prolonged release corticosteroid agent such as triamcinolone hexacetonide under microcrystalline form, because of a possible inflammatory reaction leading to necrosis of the femoral head due to hypovascularization.

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 endotrachial 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.

Use in children
For more information on use in children, see section 4.2.

Radiation synoviorthesis is indicated for use in children under 18 years of age, after a rigorous risk/benefit assessment. It must be used only in young patients if it is the only means of eliminating the progression of haemophilic arthropathy.

Special warnings
Rhenium (^{186}Re) sulphide CIS bio international contains 12.7 mg/mL of sodium.

Precautions with respect to environmental hazard see section 6.6.

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

No interaction with other medicinal products has been reported to date.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of radio-pharmaceuticals 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 any) should be offered to the patient.

If synoviorthesis is considered indispensable in woman of reproductive age, effective contraception must be instituted before administration of the radio-pharmaceutical and pursued for several months following treatment discontinuation.

Pregnancy
The use of rhenium (^{186}Re) sulphide CIS bio international is contra-indicated during pregnancy due to the radiation exposure of the foetus (see section 4.3).

Breastfeeding
The use of rhenium (^{186}Re) sulphide CIS bio international is contra-indicated during breastfeeding (see section 4.3).

Before administering a radio-pharmaceutical product to a female patient wishing to pursue breast feeding, the physician should determine whether treatment can be deferred until weaning.

4.7. Effects on ability to drive and use machines

Effects on ability to drive vehicles or to operate machines have not been described.

4.8. Undesirable effects

The following table encapsulates the types of reactions found and the symptoms, classified by organ system. The frequencies used below are defined according to the following convention:

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)

MedDRA Body system SOCs	Preferred term	Frequency
Infections and infestations	Arthritis infective	Not known
Immune system disorders	Oedema	Common
Gastrointestinal disorders	Nausea	Not known
	Vomiting	Not known
Skin and subcutaneous tissue disorders	Pigmentation disorders	Common
Musculoskeletal and connective tissue disorders	Osteonecrosis	Not known
	Joint effusion	Not known
	Joint swelling	Not known
	Arthralgia	Not known
Congenital, familial and genetic disorders	Cytogenic abnormality	Uncommon

The undesirable effects most frequently observed following radiation synoviorthesis with rhenium (^{186}Re) sulphide are:

- Brownish pigmentation of wrist at the point of injection with sometimes infiltration and sclerosis of extensor muscles in 1% of cases.
- Oedemas of forearm following wrist synoviorthesis in 1.4% of cases.
- Transient local pain or joint swelling (flare phenomenon) have been reported after joint puncture and can also occur after radiation synoviorthesis with rhenium (^{186}Re) sulphide.
- Secondary articular infection after radiation synovectomy.
- Nausea and vomiting.
- Cases of osteonecrosis.
- After rhenium (^{186}Re) sulphide synoviorthesis chromosomal aberrations have been observed in lymphocytes, in fewer proportions than what can be observed in patients undergoing radio iodine (^{131}I) thyroid therapy. For activities of 60 to 200 MBq, the amount of dicentric rings chromosomes is about 0.11%.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. In all cases it is necessary to ensure that the risks of the radiation are less than from the disease itself.

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

4.9. Overdose

In the event of overdose, the dose absorbed cannot be reduced since the physiological elimination of the radio-pharmaceutical product is very limited.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other anti-inflammatory therapeutic radio-pharmaceuticals
ATC code: V10AX05

Mechanism of action
The therapeutic activity is related to the action of beta minus radiation on the sinovial membrane. The maximum trajectory of the emitted beta minus radiation in the sinovial membrane is approximately 3 mm.

5.2. Pharmacokinetic properties

Distribution
Rhenium-186 is used in the form of a biodegradable colloidal solution with a soluble complex content of less than1%. The colloidal form of the preparation promotes phagocytosis of rhenium-186 enabling concentration in the sinovial membrane and gradually induces fibrosis of that membrane.

The colloidal form also reduces the risk of extra-articular migration. This risk may be further minimized by concomitant intra-articular administration of corticosteroids and by immobilization of the treated joint for 3 days.

After intra-articular injection, the only organs which can be seen on a total body scintigram are liver and lymph nodes for which the relative amounts of radioactivity by comparison with the radioactivity present in the total body at the same time are respectively 1.1 ± 0.9 % and 4.4 ± 5.1 % at 24 hours following administration.

5.3. Preclinical safety data

Toxicology studies have shown that a single intravenous injection of rhenium sulphide, at a dose of 2.16 mg/kg of rhenium sulphide, does not induce mortality in mice.

This product is not intended for continuous or regular administration.

Accordingly, no mutagenicity, oncogenicity/carcinogenicity or reproductive function studies have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Ascorbic acid
Gelatin
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (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

10 days from the date of manufacture.

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

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 of the medicinal product, see section 6.3.

Storage of radio-pharmaceuticals should be in accordance with national regulation on radioactive material.

6.5. Nature and contents of container

Colourless, type I 15-ml glass vials closed with ETFE coated chlorobutyl stopper and polypropylene lid welded to an aluminum crimp capsule. The vial is enclosed within a lead shield.

Pack size: 1 multi-dose vial containing 0.20 to 10 mL (37 to 3700 MBq at calibration date).

6.6. Special precautions for disposal and other handling

General warnings

Radio-pharmaceuticals should be received, used and administered only by authorised person 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.

Radio-Pharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

If at any time in the preparation of this product the integrity of the vial is compromised it should not be used.

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.

Before use, check the packaging, pH and activity.

Store the vial in its lead protective sheath. The vial must not be opened.

After disinfection of the stopper, the solution should be withdrawn through the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle.

The administration of radio-pharmaceuticals 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

Country specific

8. MARKETING AUTHORISATION NUMBER

Country specific

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Country specific

10. DATE OF REVISION OF THE TEXT

February 2026

11. DOSIMETRY

Radiation exposure may be estimated using the dosimetry tables below. The estimated radiation exposure values were determined in human subjects or based on a simulated calculation (MIRD/ICPR60/simulation Monte Carlo).

The data shown in the tables below were calculated based on the following assumptions:

It is assumed that extra-articular migration of the radio-pharmaceutical in colloidal form occurs via the lymphatic system: the colloid is initially transported to the regional lymph nodes, then to more distant lymph nodes, and finally, into the bloodstream. It is then rapidly incorporated by the reticuloendothelial system.

The results marked with an asterisk (*) were obtained using MIRDOSE 3.1 based on absorption of the dose of radiation by organs, estimated for the least favourable case, i.e. by using the dwell time [(fraction in the organ x half-life/ln2) x leak fraction] for the small-size colloids (particles < 100 nm). The median value of 10% extra-articular migration is used to estimate radiation exposure due to the action of extra-articular migration.

For the testicles, the radiation dose absorbed was determined using MIRDOSE 3.1 and adding the braking radiation (bremsstrahlung) values measured from the hip treated and the regional lymph nodes.

Table 1: Radiation dose absorbed by organs (mGy / MBq injected for 1% of extra-articular migration) and effective dose (mSv / MBq injected / % of extra-articular migration) after injection in the hip joint.

	Absorbed doses related to fixation by the reticuloendothelial system (RES)		**Doses absorbed, in mGy for 100 MBq due to fixation by the RES and to irradiation of the testicles by the supposed radioactivity present in the hip at 10 cm**
Target organ	**mGy/MBq with 1% migration**	**mGy per injection of 110 MBq with 10% migration**	
Rate*	0.137	150.7	150.7
Liver*	0.0925	101.7	101.7
Bone marrow*	0.0159	17.49	17.49
Bone surfaces*	0.00986	10.85	10.85
Uterus*	0.000208	0.23	0.23
Ovaries	0.000219	0.24	0.24+2.5 = 2.7
Testicles	0.000176	0.19	0.19+2.5 = 2.7
Kidneys*	0.000413	0.45	0.45
Other tissues	<0.001	<1.1	<1.1
Entire body	0.00348	3.83	3.83
	mSv/MBq for 1% migration	**mSv**	**mSv**
Effective dose	0.0102	11.2	11.2 + (0.2 x 2.5) = **11.7**

The lymph nodes are not included in the effective dose calculation.

Radiation doses related to fixation by the lymph nodes, after radiation synoviorthesis of the hip by rhenium sulphide (^{186}Re).

Number of lymph nodes involved	**Dose absorbed**	
	per MBq injected and for 1% of lymph node fixation (**mGy**)	Injection of 110 MBq and 3% of lymph node fixation (**Gy**)
1	234	77
2	117	39
4	59	19
8	29	10

The effective dose that results from intra-articular administration of 110 MBq of radioactivity in a hip and from 10% extra-articular migration is approximately 11.7 mSv in a subject weighing 70 kg.

For 110 MBq of radioactivity injected, the radiation doses delivered to the critical organs are: isolated lymph node with fixation rate of 3%: 77 Gy, nodal mass containing 8 lymph nodes and a 3% fixation rate: 10 Gy; testicles: 2.7 mGy; ovaries: 2.7 mGy; liver: 102 mGy; spleen: 151 mGy; kidneys: 0.45 mGy.