

Medicinal product no longer authorised

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ChondroCelect 10,000 cells/microlitre implantation suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Characterised viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins.

2.2 Qualitative and quantitative composition

Each vial of product contains 4 million autologous human cartilage cells in 0.4 ml cell suspension, corresponding to a concentration of 10,000 cells/microlitre.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Implantation suspension

Before re-suspension the cells are settled to the bottom of the container forming an off-white layer and the excipient is a clear colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults. Concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present. Demonstration of efficacy is based on a randomised controlled trial evaluating the efficacy of Chondrocelect in patients with lesions between 1-5cm².

4.2 Posology and method of administration

ChondroCelect must be administered by an appropriately qualified surgeon and is restricted to hospital use only. ChondroCelect is solely intended for autologous use and should be administered in conjunction with debridement (preparation of the defect bed), a physical seal of the lesion (placement of a biological membrane, preferentially a collagen membrane) and rehabilitation.

Posology

The amount of cells to be administered is dependent on the size (surface in cm²) of the cartilage defect. Each product contains an individual treatment dose with sufficient number of cells to treat the pre-defined lesion size, as measured at biopsy procurement. The recommended dose of ChondroCelect is 0.8 to 1 million cells/cm², corresponding with 80 to 100 microlitre of product/cm² of defect.

Elderly population

The use of ChondroCelect has not been studied in this age group.

Paediatric population

The safety and efficacy in children and adolescents (aged less than 18) have not been established. ChondroCelect is therefore not recommended for use in children and adolescents below 18 years.

Method of administration

For implantation.

ChondroCelect is intended solely for use in autologous cartilage repair and is administered to patients in an Autologous Chondrocyte Implantation procedure (ACI).

Implantation of ChondroCelect is to be performed during arthrotomy under sterile conditions and requires both preparation of the defect bed and a seal (biological membrane) to secure the implant. Complete joint haemostasis must be achieved prior to membrane fixation and cell implantation. During the ACI procedure it is important to ensure that a good, direct contact of the implanted cells with the defect bed is obtained as such contact is of paramount importance for optimal tissue regeneration. In clinical studies with ChondroCelect a periosteal flap was used as a biological membrane. Scientific publications have shown that commercially available collagen membranes can be used as an alternative to the periosteum in ACI procedures. However, ChondroCelect has not been evaluated in combination with collagen membranes in clinical studies, although a commercially available collagen membrane has been used in patients treated with ChondroCelect under compassionate use. The safety data obtained in these patients do not indicate a particular safety concern, and confirm a lower incidence of hypertrophy as suggested by scientific literature on the use of collagen membranes versus periosteum.

A technical variant of the ACI procedure is the cell seeding method, whereby the cells are seeded onto a collagen membrane prior to implantation. In this technique, a good fixation using stitches on the edges of the collagen membrane is required, in order to assure a direct contact of the implanted cells with the defect bed. Using fibrin glue only, instead of stitches, to secure the implant is not recommended.

The implantation should be followed by an appropriate rehabilitation schedule for approximately one year, as recommended by the physician (see section 4.4).

Full technical details on the procedures associated with this implantation technique are provided in the ChondroCelect user manual.

For information on preparation and handling of ChondroCelect, please refer to section 6.6.

4.3 Contraindications

Hypersensitivity to any of the excipients listed in section 6.1, or to bovine serum.

ChondroCelect must not be used in case of advanced osteoarthritis of the knee.

Patients with femoral epiphyseal growth plate that is not fully closed

4.4 Special warnings and precautions for use

General

ChondroCelect is an autologous product and should under no circumstances be administered to other patients.

Patients with acute or recent history of bone or joint infections should be temporary deferred until documented recovery.

Precautions for use

Concomitant knee problems like early osteoarthritis, osteochondritis dissecans (OCD), instability of the knee, cartilage lesions at other locations than the femoral condyle, lesions of knee ligaments or of the meniscus, varus or valgus malalignment (abnormal weight distribution in the knee), and inflammatory joint disease are potential complicating factors. In the pivotal study of ChondroCelect, patients with these comorbidities of the knee were excluded from treatment. Where possible, concomitant knee problems should be corrected prior to or at the latest at the time of ChondroCelect implantation.

In the pivotal study there was no influence of Body Mass Index (BMI) on outcome but bibliographic data shows that a BMI over 30 may adversely affect the success of the procedure.

Rehabilitation

Upon implantation, the patient should follow an appropriate rehabilitation schedule and physical activity should be resumed as recommended by the physician. Depending on the location, the size of the lesion and the patient's profile, appropriate rehabilitation instructions have been developed. Too early and vigorous activity may compromise the grafting and the durability of clinical benefit from ChondroCelect. Therefore the treated knee should be protected according to the recommendations as outlined in the appropriate rehabilitation schedule, to avoid early damage which might lead to graft failure.

Details and information on the appropriate rehabilitation schedule is provided in the ChondroCelect user manual.

Cases in which ChondroCelect cannot be supplied

In some cases it can be possible that the source chondrocytes of the patient are not expandable or that the release criteria are not met, due to poor biopsy quality, patient characteristics, or manufacturing failure. Therefore it can occur that ChondroCelect cannot be delivered. The surgeon will be informed as early in the process as possible, and should hence select an alternative treatment for the patient concerned.

4.5 Interaction with other medicinal products and other forms of interaction

Fibrin glues are routinely used in ACI procedures to seal the outside margins and to improve the water-tightness of the compartment of the biological membrane used to cover the defect. The use of fibrin glue inside the cartilage defect bed is not recommended as this may result in a significantly poorer outcome (see section 5.3).

Fibrin sealant products differ significantly in their quantitative and qualitative composition. In vitro interaction studies were performed with a commercially available fibrin glue containing aprotinin (a fibrinolysis inhibitor of bovine origin). These studies have demonstrated that this type of fibrin sealant can be safely used with ChondroCelect. No interaction studies with any other type of fibrin glues were performed. However, the concomitant use of another type of fibrin glue with a synthetic fibrinolysis inhibitor (tranexamic acid) in the pivotal clinical trial did not reveal any safety signal.

Pain relief medicinal products should be used according to the recommendations of the responsible surgeon.

4.6 Fertility, pregnancy and lactation

Pregnancy

Limited clinical data on exposed pregnancies are available. Conventional reproductive and developmental toxicity studies are not considered relevant, given the nature and the intended clinical use of the autologous cell therapy product. As ChondroCelect is used to repair a cartilage defect of the knee and is implanted with the ACI procedure using open-knee surgery, it is not recommended during pregnancy.

Breast-feeding

There are no data on the use of ChondroCelect during breast-feeding. Given the local nature of ChondroCelect adverse reactions on the nursing infant are not anticipated. A decision should be made whether to discontinue breast-feeding taking into account the potential benefits of the treatment for the woman and the potential risk to the infant.

Fertility

There are no data on possible effects of ChondroCelect treatment on fertility.

4.7 Effects on ability to drive and use machines

Due to the surgical nature of the underlying procedure, implantation with ChondroCelect has a major influence on the ability to drive and use machines. During the rehabilitation period that follows treatment with ChondroCelect, patients should refer to their treating physician and follow their advice strictly.

Driving cars and using machines may be limited during the rehabilitation period.

4.8 Undesirable effects

Summary of the safety profile

In a randomized, controlled study in the target population, 51 patients were treated with ChondroCelect. In these patients, a periosteal flap was used to secure the implant. Adverse reactions occurred in 78.4% of the patients over a 36-months postoperative follow-up period..

Related to ChondroCelect:

- arthralgia
- cartilage hypertrophy
- joint crepitation
- joint effusion
- treatment failure
- delamination

The adverse reactions listed are those that occurred most frequently, with treatment failure and delamination being the most serious.

Related to surgical intervention of the knee

- (postoperative) joint swelling
- arthralgia
- pyrexia
- arthrofibrosis
- decreased range of motion of the knee

Most of the reported adverse reactions were expected as related to the open-knee surgical procedure.. These were generally mild and disappeared in the weeks following surgery.

Tabulated list of adverse reactions

They are listed by System Organ Class and frequency. Frequencies are defined according to the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Very common $\geq 1/10$	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1,000$ to $< 1/100$
Vascular disorders		Deep vein thrombosis, Haematoma, Superficial phlebitis	Fat embolism, Thrombophlebitis
Respiratory, thoracic and mediastinal disorders		Apnoea	Lung embolism
General disorders and administration site conditions		Ineffective therapeutic product, Gait disturbance,	Atrophy, Discomfort, Granulomatous lesion

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
		Impaired healing, Implant site hypersensitivity, Peripheral edema, Pyrexia	
Injury, poisoning and procedural complications		Graft complication, Graft delamination, Cartilage injury, Injury, Joint injury, Procedural site reaction	
Musculoskeletal and connective tissue disorders	Arthralgia, Cartilage hypertrophy, Joint crepitation, Joint swelling	Arthrofibrosis, Joint range of motion decreased, Joint effusion, Joint lock, Arthritis, Arthropathy, Bone cyst, Bone swelling, Bursitis, Chondropathy, Exostosis, Haemarthrosis, Joint instability, Joint stiffness, Loose body in joint, Mobility decreased, Muscle atrophy, Osteoarthritis, Synovial cyst, Synovitis, Tendon disorder, Tendonitis	Chondromalacia, Gonarthrosis
Nervous system disorders		Autonomic neuropathy, Complex regional pain syndrome, Pain in extremity, Peripheral neuropathy, Syncope, Trendelenburg's symptom	Hyperesthesia, Migraine, Photophobia, Transient ischaemic attack
Investigations		Arthroscopy	
Skin and subcutaneous tissue disorders		Wound infection, Erysipelas, Erythema, Hypertrophic scar, Postoperative wound complication, Pruritus, Scar pain, Wound dehiscence, Wound secretion	Itching scar

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Psychiatric disorders			Anxiety
Gastrointestinal disorders		Nausea	

Description of selected adverse reactions

Arthrofibrosis

In the compassionate use patients, a higher incidence of arthrofibrosis and decreased joint range of motion was observed in a subgroup of patients with a patellar lesion (8.2% and 13.1% respectively) compared to non-patellar lesions (0.6% and 2.6% respectively).

Cartilage hypertrophy

In the majority of the 370 patients included in the Compassionate Use Program, a collagen membrane instead of a periosteal flap was used to seal the defect. According to current literature the incidence of cartilage hypertrophy can be reduced by using a collagen membrane to cover the lesion site instead of using a periosteal flap (Gooding *et al.*, 2006; Niemeyer *et al.*, 2008). When a collagen membrane was used to seal the lesion site after application of ChondroCelect, the incidence of cartilage hypertrophy was reported to be 1.8% compared to 25% in the randomized, controlled trial alone.

Synovitis and *subchondral bone injuries* have been reported in animal models and are possible risks with the use of ChondroCelect.

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 listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for disorders of the musculo-skeletal system, ATC code: M09AX02

Conventional pharmacodynamic studies for ChondroCelect have not been performed.

Clinical efficacy

The efficacy of ChondroCelect was studied in a phase III, multicenter, randomized, controlled trial (TIG/ACT/01/2000) and the first two years of its 4-year extension phase (TIG/ACT/01/2000EXT). ChondroCelect was compared to the procedure of microfracture in the repair of symptomatic single cartilage lesions of the femoral condyles of the knee. 51 patients were treated with ChondroCelect, 61 patients were treated with microfracture. Patients aged between 18 and 50 years, who had a single symptomatic cartilage lesion between 1 and 5 cm² of the femoral condyles met the inclusion criteria. Patients could be treatment-naïve or might have undergone previous arthroscopic or other surgical repair procedure(s). Patients with patellofemoral cartilage lesion, OCD, depth of lesion >0.5 cm, prior meniscal transplant, prior mosaicplasty and prior microfracture within the last 12 month were

excluded. Patients had to agree to actively participate in a strict rehabilitation protocol and follow-up program.

The median time since onset of knee injury was slightly longer in the ChondroCelect group than in the microfracture group (2.0 years versus 1.6 years). More patients in the ChondroCelect treatment group, compared to patients in the microfracture group, had undergone previous knee surgery (88% versus 77%). In the ChondroCelect group 77% of patients had a medial and 23% a lateral condyle defect.

Histological examination of the repair biopsy at 12 months showed superior structural repair in the ChondroCelect arm compared to the microfracture arm. There was continuous improvement up to 36 months in the clinical outcome measure KOOS (the Knee Injury and Osteoarthritis Outcome Score) in both treatment arms. The estimated benefit was larger in the ChondroCelect group but the results did not reach statistical significance. At this time point 41 patients were evaluated in the ChondroCelect arm and 49 were evaluated in the microfracture arm. Patients with less than 3 years since onset of symptoms (n=27 in the ChondroCelect arm and n=32 in the microfracture arm) benefited most from ChondroCelect. For the group with a longer time since onset of symptoms there were no apparent differences between the 2 groups. Re-intervention on the treated lesion for graft delamination or periost loosening occurred in 2 of 51 patients within 36 months after ChondroCelect implantation, compared to 7 of 61 patients treated with microfracture having generally insufficient or inadequate cartilage repair.

After the 5 year follow-up period, 37 patients were evaluated in the ChondroCelect arm and 40 in the microfracture arm. Overall, the clinically relevant benefit of ChondroCelect implantation observed over baseline after 36 months was maintained up to 60 months after treatment. No statistically significant difference could be observed in clinical benefit between ChondroCelect and microfracture at that point in time. In the subgroup of patients with recent symptom onset (< 3 years) the clinical benefit of ChondroCelect over microfracture was significantly larger, confirming the results at 36 months after treatment. In patients with a longer time since onset of symptoms, both treatments performed equally. Seven patients treated with ChondroCelect needed re-intervention, compared to 10 patients in the microfracture group. Treatment failure in the ChondroCelect group was generally related to delamination of the graft.

Patients with lesions larger than 5 cm² have been treated under compassionate use only. The safety data obtained in these patients do not indicate a particular safety concern. Further clinical data in patients with larger lesions are foreseen to be collected in the future.

Sixteen patients below 18 years have been treated with ChondroCelect under compassionate use. No specific safety signal was detected in these patients. If, based on the benefit/risk assessment of the responsible surgeon treatment of patients below 18 years is considered, special attention should be given to ensure that the growth plate is completely closed.

5.2 Pharmacokinetic properties

The product is implanted locally.

The nature and intended clinical use of ChondroCelect are such that conventional studies on pharmacokinetics, absorption, distribution, metabolism and elimination are not applicable.

5.3 Preclinical safety data

Non-clinical data based on implantation of expanded cartilage cells in goats and mice did not reveal special hazard for humans.

In studies in goats, mild signs of synovitis were observed in the majority of the animals, including controls at 10 weeks post surgery. Inflammation resolved with time and parameters returned to baseline levels with only some very mild and local signs of synovitis remaining in a few animals.

Although it is thought that these reactions are mostly surgery-related, a potential influence of the expanded chondrocytes cannot be completely excluded.

In a study in sheep, the majority of animals showed penetration of the transplanted cells in subchondral bone; in two of these cases complete penetration of underlying bone marrow was observed. This finding might be related to the inability to perform a progressive loading under non-weight bearing conditions post-surgery in these models and therefore cannot be fully extrapolated as such to the human situation.

A technical variant of the ACI procedure is the cell seeding method, whereby the cells are seeded onto a collagen membrane prior to implantation. From a pre-clinical study in the orthotopic goat model it appeared that this technique provided comparable results as the Brittberg technique, on condition that a good fixation is established using stitches on the edges of the collagen membrane. Using fibrin glue in the defect bed instead of stitches to secure the implant resulted in an overall poor outcome, suggesting the need for a direct contact of the implanted cells with the defect bed

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dulbecco's Modified Eagles Medium (DMEM) (containing amino acids, vitamins, salts and carbohydrates).

6.2 Incompatibilities

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

6.3 Shelf life

48 hours.

6.4 Special precautions for storage

Store between 15°C – 25°C.

Do not refrigerate or freeze.

Keep the product vial(s) within the falcon tube in the outer plastic screw top container in order to protect from light and bacterial/fungal contamination.

Do not irradiate.

6.5 Nature and contents of container and special equipment for use, administration or implantation

ChondroCelect is supplied as one individual treatment dose (falcon tube) contained in 1 to 3 Type I glass vials of 1 ml. Each vial contains 0.4 ml of autologous human cartilage cells suspension and is closed with a chlorobutyl stopper and aluminium seal.

The vials are placed in a sterile falcon tube with a plastic screw top.

The falcon tube is placed in a plastic screw top container together with surgery materials (one sterile syringe of 1 ml, one 18G intravenous catheter and two pieces of Vicryl 6.0) and a temperature monitor.

6.6 Special precautions for disposal and other handling

ChondroCelect is intended solely for autologous use. Prior to implantation match the patient name to the patient/donor identification on the shipment documentation and product vial.

Before administration, ChondroCelect should be resuspended by gently tapping the vial to bring the cells back into suspension.

ChondroCelect should not be sterilised. If the ChondroCelect vial is damaged or its sterility has been compromised, the product must not be used and must be shipped back to TiGenix.

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

7. MARKETING AUTHORISATION HOLDER

TiGenix N.V.
Romeinse straat 12/2
3001 LEUVEN
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/563/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5 October 2009
Date of latest renewal: 22 August 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

PharmaCell Cell Manufacturing Facility B.V.
Urmonderbaan 20B
6167 RD Geleen
Netherlands

Name and address of the manufacturer(s) responsible for batch release

TiGenix N.V.
Romeinse straat 12/2
B-3001 LEUVEN
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex 1: Summary of Product Characteristics, section 4.2).

The Marketing Authorisation Holder (MAH) shall ensure that the medicinal product will be distributed only to Healthcare Establishments that meet criteria described in the Risk Management Plan.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Pharmacovigilance system**

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

The marketing authorisation holder shall submit the periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the pharmacovigilance activities as agreed in the RMP presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
 - Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile
- If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure, prior to the distribution of the product to a particular healthcare establishment, that all surgeons and other healthcare professionals involved in the handling and administration of ChondroCelect or its components, as well as those involved in follow-up of patients treated with ChondroCelect in the healthcare establishment, receive training as per the educational programme described in the risk management plan.

The educational programme for healthcare professionals contains the following components:

- Training material for surgeons
- Training material for other healthcare professionals
- Informed consent for the patients to be signed prior to the treatment with ChondroCelect

The training materials for surgeons shall include the following key messages and components:

- Summary of Product Characteristics
- The biopsy harvest procedure
- The surgical checklist to be completed at the operating theatre immediately prior to the first incision confirming the right patient, the right product, the right side of the implantation, and the type of biological membrane and fibrin sealant to be used in the procedure.
- The implantation procedure by knee-joint arthrotomy
- The follow-up protocol

The training material for other healthcare professionals shall include the following key messages and components:

- Summary of Product Characteristics
- The need for screening of donors using patient questionnaire and laboratory tests for hepatitis C, hepatitis B, HIV, and syphilis
- The handling of the biopsy harvest
- The handling of ChondroCelect and its preparation for the implantation
- The schedule of follow-up of patients
- The recommended physiotherapy

- **Obligation to conduct post-authorisation measures**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

White screw top container

1. NAME OF THE MEDICINAL PRODUCT

ChondroCelect 10,000 cells/microlitre implantation suspension.

Characterised viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 4 million autologous human cartilage cells in 0.4 ml, corresponding to a concentration of 10,000 cells/microlitre.

3. LIST OF EXCIPIENTS

Dulbecco's Modified Eagles Medium (DMEM).

4. PHARMACEUTICAL FORM AND CONTENTS

Implantation suspension.

1 falcon tube with 1, 2 or 3 vials (x 0.4 ml)

Vials are supplied with surgery materials (one sterile syringe of 1 ml, one 18G IV catheter and two pieces of Vicryl 6.0 sutures)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For implantation.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP {DD month YYYY} at {hours} CET

9. SPECIAL STORAGE CONDITIONS

Store between 15°C – 25°C.

Do not refrigerate or freeze.

Keep the product vial(s) within the falcon tube in the outer plastic screw top container in order to protect from light and bacterial/fungal contamination.
Do not expose to radioactive irradiation (X-rays).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TiGenix N.V., Romeinse straat 12/2, 3001 Leuven, Belgium
Tel: +32-(0)16 39 60 60
Fax: +32-(0)16 39 60 70
info@tigenix.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/563/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot {lot number}
Patient number (Pt N°) {patient number}
Patient initials (Pt initials) {patient initials}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL INTERMEDIATE PACKAGING UNITS

Falcon tube

1. NAME OF THE MEDICINAL PRODUCT

ChondroCelect 10,000 cells/microlitre implantation suspension.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {DD month YYYY} at {hours} CET

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot {lot number}

Pt N° {patient number}

Pt initials {patient initials}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1, 2 or 3 vials x 0.4 ml

6. OTHER

For autologous use only.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT

ChondroCelect

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {DD month YYYY} at {hours} CET

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot {lot number}

Pt N° {patient number}

Pt initials {patient initials}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

For autologous use only.

B. PACKAGE LEAFLET

Medicinal product no longer authorised

Package leaflet: information for the user

ChondroCelect 10,000 cells/microlitre implantation suspension

Characterised viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, surgeon or physical therapist.
- If you get any of the side effects, talk to your doctor, surgeon or physical therapist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ChondroCelect is and what it is used for
2. What you need to know before you use ChondroCelect
3. How to use ChondroCelect
4. Possible side effects
5. How to store ChondroCelect
6. Contents of the pack and other information

1. What ChondroCelect is and what it is used for

ChondroCelect consists of autologous cultured cartilage cells. The product is made from a small sample of cartilage cells (a biopsy) taken from your knee.

- **Autologous** means that your own cells are used to make ChondroCelect.
- **Cartilage** is a tissue that is present in every joint. It protects the ends of our bones and allows our joints to function smoothly.

ChondroCelect is used to repair single symptomatic cartilage defects in the femoral condyle of the knee in adults. A defect can be caused by acute trauma, such as a fall. It can also be caused by repetitive trauma, as a result of overweight or due to incorrect weight-bearing on the knee as a result of a knee deformity.

- The **femoral condyle** is the end of the thigh bone, which forms part of your knee.

2. What you need to know before you use ChondroCelect

Do not use ChondroCelect if you:

- are allergic to any of the ingredients of ChondroCelect (listed in section 6) or to bovine serum
- suffer from advanced osteoarthritis (degenerative joint disease) in your knee.
- have a growth plate of the knee that is not fully closed

Warnings and precautions

Talk to your doctor, surgeon or physiotherapist before using ChondroCelect.

- If you have an acute or recent history of bone or joint infections, you should be temporary deferred until documented recovery.

- The use of ChondroCelect is generally not recommended when you are overweight (i.e. a Body Mass Index over 30) because it could compromise the result of the treatment. Your surgeon will give you more information.
- ChondroCelect is not recommended for the repair of cartilage defects in other locations than the femoral condyle.
- ChondroCelect should be implanted in an otherwise healthy knee. This means that other knee problems such as lesions of the knee ligament or of the meniscus should be corrected before or during ChondroCelect implantation.
- You should resume physical activity according to the rehabilitation plan recommended by the physical therapist. Too early and vigorous activity may compromise the implant and the durability of clinical benefit from ChondroCelect.

Other cases in which ChondroCelect cannot be supplied

Even if the surgeon has already taken a small sample of cartilage cells (a biopsy) needed to produce the product, it is possible that you will not be eligible for treatment with ChondroCelect. This is the case if the biopsy is of insufficient quality to make ChondroCelect, or in some instances, it may be the cells cannot be grown in the laboratory or that the cells after expansion do not meet all the quality requirements. Your surgeon will be informed and might have to select an alternative treatment for you.

Children and adolescents

The use of ChondroCelect is not recommended in children and adolescents below 18 years.

Other medicines and ChondroCelect

Please tell your doctor or physical therapist if you are taking, have recently taken or might take any other medicines.

The safe use of ChondroCelect with other medicines has not been studied.

Ask your doctor for more information as to which pain medication you can safely use.

Pregnancy and breast-feeding

The safe use of ChondroCelect has not been demonstrated during pregnancy or breast-feeding.

ChondroCelect is not recommended for pregnant and breast-feeding women.

Please inform your doctor if you are pregnant or think you may be pregnant.

Driving and using machines

The surgical procedure will have a major influence on your ability to drive and use machines. Driving cars and using machines may be limited during the rehabilitation period, and the advice of your doctor, surgeon or physical therapist should be strictly followed during this period.

3. How to use ChondroCelect

ChondroCelect can only be prescribed and implanted by an orthopaedic surgeon in a hospital.

Treatment with ChondroCelect: a two-step procedure.

Visit 1: evaluation of the cartilage defect and biopsy

On the first visit, the surgeon will evaluate your cartilage defect during an exploratory operation (arthroscopy). An arthroscopy is performed through very small incisions in the skin, using a narrow telescope (arthroscope) to look at the inside of the knee. If the surgeon decides that treatment with ChondroCelect is appropriate for you, he/she will take a small sample of cartilage cells (a biopsy) from your knee. This cartilage sample will be used to make ChondroCelect.

It will take at least four weeks to select and culture the cells to make ChondroCelect.

Visit 2: ChondroCelect implantation

During open-knee surgery, the cartilage cells are implanted into the cartilage defect. This is called 'autologous chondrocyte implantation' (ACI). The purpose is to repair the defect with healthy and functional cartilage over time.

To keep the cartilage cells in place, a biological membrane is sewn over the defect.

Rehabilitation

After surgery, you will have to follow a rehabilitation program for approximately one year, to allow your knee to heal well. Your doctor or physical therapist will give you more details on your rehabilitation.

It is very important to carefully observe the recommendations of your doctor and/or physical therapist. If you do not follow your rehabilitation schedule, the risk of treatment failure may increase.

You should be very cautious when bending and putting weight on your treated knee. During the rehabilitation period, the level of weight-bearing will increase gradually, depending on your weight and the size of the cartilage defect. To protect your knee, you will have to wear a brace.

If you have any further questions on the use of this medicine, ask your doctor or physical therapist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most side effects of ChondroCelect implantation are side effects related to open-knee surgery. In general, these side effects are quite mild and disappear in the weeks following surgery.

You can recognize most of the joint- related side effects if you have symptoms like pain, snapping, grinding, locking, swelling, bending limitations and stiffness in the knee. Tell your doctor immediately if you notice any of these symptoms.

Very common side effects (affects more than 1 user in 10) include: joint pain (arthralgia), overgrowth of cartilage cells (cartilage hypertrophy), crackling or clicking sensation when articulating the knee (joint crepitation), and joint swelling.

Common side effects (affects in 1 to 10 users in 100) include: restriction of knee motion (arthrofibrosis, decreased joint range of motion, decreased mobility), excessive amount of joint fluid in the joint (joint effusion), joint lock, joint inflammation (arthritis, bursitis, synovitis), cavity filled with fluid in the knee (bone cyst, synovial cyst), bone swelling, cartilage disorder (chondropathy), benign bony growth (exostosis), blood in a joint (haemarthrosis), joint instability, joint stiffness, loose body in joint, weakening of muscle (muscle atrophy, Trendelenburg's sign), degenerative joint disorder (osteoarthritis), tendon disorder, inflammation of the tendon (tendonitis), impaired healing, treatment failure, gait disturbance, implant site hypersensitivity, peripheral edema, fever (pyrexia), postoperative wound complication (wound site reaction) ,wound infection (including erysipelas), redness, scar overgrowth, itching, scar pain, wound loosening, wound secretion loosening of the graft or membrane (graft complication, graft delamination), injury (cartilage injury, joint injury), blood clot in the deep vein of the leg (deep vein thrombosis), large bruise (haematoma), superficial vein inflammation (phlebitis), nausea, pain or nerve disorder (pain in extremity, peripheral neuropathy, complex regional pain syndrome, autonomic neuropathy), syncope, apnea, arthroscopy.

Uncommon side effects (affects in 1 to 10 users in 1,000 include: anxiety, dermal and visual hypersensitivity), migraine, mini stroke (transient ischaemic attack), fat entering the circulatory system (fat embolism), vein blockage and inflammation (thrombophlebitis), blockage in a lung artery (lung embolism), itching scar, pain at the front of the knee (chondromalacia), breakdown of knee tissue (gonarthrosis, atrophy), discomfort, chronic inflammation (granulomatous lesion).

Reporting of side effect

If you get any side effects, talk to your doctor or physical therapist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ChondroCelect

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the container and vial after EXP.

Store between 15°C – 25°C.

Do not refrigerate or freeze.

Keep the product vial(s) within the falcon tube in the plastic screw top container in order to protect from light and bacterial/fungal contamination.

Do not irradiate.

Since this product will be used during your knee surgery, the hospital staff is responsible for the correct storage of the product both before and during its use, as well as for the correct disposal

6. Contents of the pack and other information

What ChondroCelect contains

- The active substance of ChondroCelect consists of a treatment dose of viable autologous human cartilage cells in vials containing 4 million cells in 0.4 ml, corresponding to a concentration of 10,000 cells/microlitre.
- The other ingredient is sterile, buffered Dulbecco's Modified Eagles Medium (DMEM), a liquid containing amino acids, vitamins, salts and carbohydrates to store the cells in the vial.

What ChondroCelect looks like and contents of the pack

ChondroCelect is a cell suspension (a fluid) for implantation. The cells are kept alive in a small sterile vial. The product is packaged in several layers of packaging material which guarantee sterility and stable temperature conditions for 48 hours if stored at room temperature.

Each pack contains an individual treatment dose consisting of 1 to 3 vials, depending on the number of cells needed to treat the specific lesion size.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

TiGenix N.V.

Romeinse straat 12/2, 3001 LEUVEN

Belgium

+32 16 39 60 60

+32 16 39 60 70

info@tigenix.com

Manufacturer:

PharmaCell Cell Manufacturing Facility B.V., Urmonderbaan 20B, 6167 RD Geleen, Netherlands

The leaflet was approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

Medicinal product no longer authorised

Annex IV

Grounds for one additional renewal

Medicinal product no longer authorised

Grounds for one additional renewal

Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of ChondroCelect remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

Only 907 patients have been exposed up to now, including patients treated with ChondroCelect within the clinical trials conducted to support the MA of ChondroCelect. Post-marketing experience with respect to patient number, i.e. 444 patients and duration of follow-up is still quite limited, and doesn't warrant granting a renewal with unlimited validity.

The CHMP decided that the MAH should continue to submit 1-yearly PSURs.

Therefore, based upon the safety profile of ChondroCelect, which requires the submission of 1-yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years' time.

Medicinal product no longer authorised