

Medicinal product no longer authorised

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

MACI 500,000 to 1,000,000 cells/cm² implantation matrix

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each implant contains matrix applied characterised autologous cultured chondrocytes.

2.1 General description

Characterised viable autologous chondrocytes expanded *ex vivo* expressing chondrocyte-specific marker genes, seeded onto a CE marked porcine derived Type I/III collagen membrane.

2.2 Qualitative and quantitative composition

Each implantation matrix consists of characterised autologous chondrocytes on a 14.5 cm² Type I/III collagen membrane, at a density of 500,000 to 1,000,000 cells per cm², to be trimmed by the surgeon to the size and shape of the defect.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Implantation matrix.

The implant is an opaque, off-white membrane, seeded with chondrocytes, supplied in 18 ml of colourless solution in a dish.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MACI is indicated for the repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3-20 cm² in skeletally mature adult patients.

4.2 Posology and method of administration

MACI is intended for autologous use only.

MACI must be administered by a surgeon specifically trained and qualified in the use of MACI.

Posology

The amount of MACI administered is dependent upon the size (surface in cm²) of the cartilage defect. The implantation matrix is trimmed by the treating surgeon to the size and shape of the defect, to ensure the damaged area is completely covered, and implanted cell-side down. The administered dose corresponds to 500,000 to 1,000,000 autologous cells/cm² of implantation matrix.

Special populations

Older people (over 65 years of age)

The use of MACI in this age group has not been studied. The use of MACI in elderly with generalised degeneration of the cartilage or osteoarthritis is not recommended.

Paediatric population

The safety and efficacy of MACI in children less than 18 years of age have not been established. No data are available.

Method of administration

For implantation.

The defect bed should be debrided only down to the subchondral plate and not through it. Bleeding through the subchondral plate should be avoided, but if it occurs, it must be controlled. Epinephrine or fibrin sealant (see section 4.5), applied sparingly directly to bleeding points, is a suitable haemostatic agent.

Implantation of MACI is performed using sterile surgical techniques and requires both the preparation of the defect bed and the application of fibrin sealant to the base and rim of the defect in order to secure the implant. At the surgeon's discretion, a few interrupted absorbable sutures may also be used to provide extra security.

The implantation should be followed by an appropriate rehabilitation schedule (see section 4.4).

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

4.3 Contraindications

- Hypersensitivity to any of the excipients listed in section 6.1, or porcine products, or any residual component carried over from manufacture of MACI, including bovine serum, and gentamicin.
- Severe osteoarthritis of the knee.
- Inflammatory arthritis, inflammatory joint disease, or uncorrected congenital blood coagulation disorders.
- Patients with a femoral epiphyseal growth plate that is not fully closed.

4.4 Special warnings and precautions for use

General

MACI is an autologous implant and must only be administered to the patient for whom it was manufactured. Implantation of MACI is to be performed during arthrotomy under sterile conditions. There is limited experience with delivery of MACI to the knee via arthroscopy, however, arthroscopic techniques may be used to apply MACI at the discretion of the treating physician.

Precautions for use

Patients with local inflammations or active infections in the bone, joint, and surrounding soft tissue should be temporarily deferred until documented recovery.

In the pivotal study of MACI, patients were excluded if they had a history of osteoarthritis (Kellgren-Lawrence Grade 3 or 4) in the target knee, or concomitant inflammatory disease.

To create a favourable environment for healing, concomitant pathologies must be addressed prior to or concurrent with implantation of MACI. These include:

- Meniscal pathology: unstable or torn meniscus requires repair, replacement, or partial meniscectomy. MACI is not recommended in patients with a total meniscectomy unless the meniscal deficiency can be addressed with a staged or concurrent meniscal graft.
- Cruciate ligament instability: the joint should not possess excessive laxity. Both anterior and posterior cruciate ligaments should be stable or undergo reconstruction to reduce shearing forces and rotation stresses across the joint.
- Malalignment: the tibio-femoral joint should be properly aligned. Abnormal varus or valgus loading of the tibio-femoral joint may jeopardise the implant and should be addressed with a corrective osteotomy or similar procedure. When treating trochlear and patellar defects, abnormal patellar tracking must be corrected, prior to or concurrent with MACI implantation.

Post-operative haemarthrosis occurs mainly in patients with a predisposition to haemorrhage or poor surgical haemorrhage control. The patient's haemostatic functions should be screened prior to surgery. Thromboprophylaxis should be administered according to local guidelines.

Local treatment guidelines regarding the use of antibiotic prophylaxis around orthopaedic surgery should be followed.

Due to limited experience, the use of MACI in joints other than the knee is not recommended.

MACI is shipped following a validated rapid microbial sterility assay to determine absence of microbial growth. Final sterility test results are not available at the time of shipping. If positive sterility results are obtained, the treating physician will be contacted to discuss either cancellation of the implantation or a plan of action based on the patient-specific circumstances and risk assessment.

Rehabilitation

Controlled physiotherapy, including early mobilisation, range-of-motion exercises, and partial weight-bearing is recommended as soon as possible to promote graft maturation and to reduce the risk of post-operative thromboembolic events and joint stiffness. Following implantation, the patient should follow an appropriately controlled, phased rehabilitation programme as recommended by the treating physician based on the MACI Rehabilitation Manual. This should include specified or staged physical activity in order to minimise the likelihood of arthrofibrosis and graduated partial weight-bearing. Return to sporting activity should be personalised in consultation with healthcare professionals.

Cases in which MACI cannot be supplied

In some cases, it may occur that source chondrocytes of the patient are not expandable or that the release criteria (see section 6.6) are not met due to poor biopsy quality, patient characteristics, or manufacturing failure. Therefore, it may occur that MACI cannot be delivered.

4.5 Interaction with other medicinal products and other forms of interaction

Fibrin sealants containing formaldehyde must not be used with MACI, since formaldehyde is cytotoxic to the chondrocytes.

While oral use of pain medication is recommended for post-surgical pain relief, intra-articular administration of analgesics is not recommended as studies have shown adverse effects on articular cartilage and chondrocytes with exposure.

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 medicinal product. Given the local nature of the medicinal product, adverse reactions of MACI on pregnancy are not anticipated. However as MACI will be implanted using invasive surgical techniques, it is not recommended during pregnancy.

Breast-feeding

There are no data on the use of MACI during breast-feeding. Given the local nature of the product, adverse reactions of MACI on the nursing infant are not anticipated. However as MACI will be implanted using invasive surgical techniques, a decision must be made whether to discontinue breast-feeding taking into account the benefits of treatment for the woman and the risk to the infant.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Based on the exposure of more than 6,000 patients to MACI treatment in the knee, complications may be related to the arthrotomy procedure, general complications related to surgical intervention, other knee pathology (such as ligamentous or meniscal pathology), or the biopsy procurement. Complications related to knee surgery in general may also include deep vein thrombosis and pulmonary embolism. Other complications have been identified as causally related to MACI. The following important risks have been identified related to either MACI or peri-operative complications:

Related to MACI:

- Symptomatic graft hypertrophy
- Graft delamination (complete or partial, possibly leading to loose bodies in the joint or graft failure)

Peri-operative complications related to surgical intervention of the knee:

- Haemarthrosis
- Arthrofibrosis
- Localised surgical site inflammation
- Localised surgical site infection
- Thromboembolic events

Tabulated list of adverse reactions

Adverse reactions 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 ($< 1/10,000$).

System organ class	Uncommon	Rare
Infections and infestations		Infective arthritis Wound infection Localised infection
Musculoskeletal and connective tissue disorders		Arthrofibrosis Synovitis Tendonitis Haemarthrosis Arthralgia Joint effusion Joint swelling Joint stiffness Bone oedema Joint range-of-motion decreased
General disorders and administration site conditions		Inflammation Hyperthermia Pyrexia Implant site oedema
Investigations		C-reactive protein increased
Injury, poisoning and procedural complications	Graft delamination Graft complication Graft hypertrophy	Graft loss Cartilage injury

Description of selected adverse reactions

Graft delamination:

Graft delamination refers to a loosening, either partial or total, of the graft from the subchondral bone and from the surrounding cartilage. A total graft delamination is a serious complication and the patient may experience locking, pain, and swelling after an acute distortion of the knee.

Risk factors for graft delamination can include but are not limited to poor patient selection, poor adherence to recommended surgical technique, failure to address concomitant pathologies, poor compliance with the rehabilitation protocol or post-operative trauma to the knee.

Graft hypertrophy:

Symptomatic graft hypertrophy is a complication that may occur with MACI.

Symptoms may include catching or pain. There are no known risk groups or specific risk factors for graft hypertrophy in patients treated with MACI. Patients may require debridement of the hypertrophic tissue via arthroscopy.

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

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Medicines for Disorders of the Musculo-Skeletal system, ATC code: M09AX02

Clinical pharmacology studies have not been conducted on MACI. Current clinical and nonclinical evidence suggests that delivery of autologous chondrocytes on the collagen membrane promotes proliferation and re-differentiation of seeded cells, and may result in synthesis of hyaline-like cartilage repair tissue.

MACI has been investigated in a parallel, randomised, open-label trial in 144 patients with Outerbridge Grade III or IV focal cartilage defects of the knee of 3-20 cm² (median 4 cm²). Seventy-two patients received MACI, and 72 were treated with microfracture. The median age of patients was 34 to 35 years (age range: 18 to 54), and the mean body mass index was 26. The majority of patients had undergone at least 1 prior orthopaedic knee surgery. MACI was superior compared to microfracture regarding the improvement of pain and function according to the KOOS scale (Knee Injury and Osteoarthritis Outcome Score). See responder rates in Table 1 below.

Four patients were treatment failures in the microfracture treatment arm, versus one in the MACI treatment arm. There were no significant differences observed in the structural markers of cartilage repair between both treatments, as assessed by International Cartilage Repair Society (ICRS) II overall assessment histology scores of biopsies, and MRI defect fill scores.

Table 1: KOOS Response Rate*: Full Analysis Set

n (%)	MACI N=72	Microfracture N=72	p-value
Visit 10 (Week 104) Stratified by centre			
Responded	63 (87.50)	49 (68.06)	0.016
Not Responded	9 (12.50)	20 (27.78)	
Missing	0	3 (4.17)	
Visit 10 (Week 104) Unstratified			
Responded	62 (86.11)	48 (66.67)	0.011
Not Responded	7 (9.72)	18 (25.00)	
Missing	3 (4.17)	6 (8.33)	

* KOOS Response Rate: Responder is defined as an improvement of the Knee Injury and Osteoarthritis Outcome Score from baseline of minimal 10 points of a scale of 100.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with MACI in paediatric patients from the closure of the femoral epiphyseal growth plate to less than 18 years of age. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Typical clinical pharmacokinetic (ADME) studies have not been performed on MACI. The pharmacokinetic behaviour of MACI is related to the resorption of the collagen membrane, a proteolytic process performed by cells in the vicinity of the defects. The membrane is resorbed over the months following implantation.

5.3 Preclinical safety data

Non-clinical data based on implantation of MACI in rabbits and horses did not reveal any special hazard for humans.

Non-clinical *in vitro* investigations have shown that the collagen membrane is non-cytotoxic, non-mutagenic, non-reactive (short- and long-term implantation), non-sensitising, a negligible irritant, and non-toxic (acute systemic).

A rabbit study demonstrated that at 3 months post-implantation, minimal numbers of inflammatory cells were present in the vicinity of the defect, with variable chondrogenesis. In a horse study, signs of a minor inflammatory response, characterised by a slight increase in synovial fluid volume and a mild lymphoid accumulation in the synovium, were observed at 3 months. By 6 months, these signals had subsided, resulting in a normal synovial appearance. There were no indications of gross inflammatory reaction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dulbecco's Modified Eagles Medium (DMEM; Calcium Chloride anhydrous, Ferric Nitrate.9H₂O, Potassium Chloride, Magnesium Sulphate anhydrous, Sodium Chloride, Sodium Bicarbonate, Potassium Phosphate Monobasic.H₂O, D-Glucose, L-Arginine.HCl, L-Cystine.2HCl, L-Glutamine, Glycine, L-Histidine.HCl.H₂O, L-Isoleucine, L-Leucine, L-Lysine.HCl, L-Methionine, L-Phenylalanine, L-Serine, L-Threonine, L-Tryptophan, L-Tyrosine.2Na.2H₂O, L-Valine, D-Calcium Pantothenate, Choline Chloride, Folic Acid, i-Inositol, Niacinamide, Riboflavin, Thiamine.HCl, Pyridoxine.HCl) with 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid sodium (HEPES) adjusted for pH with HCl or NaOH and osmality with NaCl.

6.2 Incompatibilities

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

6.3 Shelf life

6 days.

6.4 Special precautions for storage

Keep MACI in the outer carton until ready to use. Do not refrigerate or freeze. Store shipping box in an area below 37°C.

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

MACI is shipped in custom-designed, sterile, sealed, clear polystyrene dishes.

Each dish contains 1 implantation matrix, held in place by a green polycarbonate x-ring and closed with a green polycarbonate cover for shipment.

Each dish is sealed in a gamma-irradiated clear plastic bag.

MACI is supplied in 1 to 2 dishes, which are placed into a 95kPa pouch (outer bag) with absorbent material for transport.

This package is enclosed in an outer carton insulated with ambient gel packs.

6.6 Special precautions for disposal and other handling

During the first procedure, a sample of healthy cartilage tissue (a biopsy) will be taken from the affected joint by an arthrotomy or arthroscopy.

The biopsy will be sent to the cell processing facility. At the cell processing facility, the cartilage cells will be grown aseptically in culture to expand the number of cells and placed onto a sterile CE marked porcine derived type I/III collagen membrane, to make MACI. MACI will be released following

successful results from assays which assess chondrocyte viability, identity, potency, minimum cell number, endotoxin, pre-release sterility, and mycoplasma.

MACI will be sent to the treatment facility. At this time, MACI will be implanted into the cartilage defect in the affected joint via a second procedure. The MACI implant will be secured in place using a fibrin sealant.

The timing between the removal of the biopsy and MACI implantation can vary depending on logistical factors in addition to the quality and number of cells obtained from the biopsy. The minimum amount of time is 6 weeks; however, cells can also be cryopreserved and held in storage for up to 24 months until a surgical date is established.

The surgeon will organise the date for MACI implantation in consultation with the Marketing Authorisation Holder (MAH) or its local representative. In rare cases the MAH will not be able to produce a MACI implant from the available cells. If this occurs, the surgeon will advise the patient on the best course of action.

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

Please consult the Surgical Technique Manual for further information.

7. MARKETING AUTHORISATION HOLDER

Vericel Denmark ApS
Amaliegade 10
DK-1256 Copenhagen K
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/847/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 June 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal 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 of the biological active substance

Genzyme Biosurgery ApS
Oliefabriksvej 45
DK - 2770 Kastrup
Denmark

Name and address of the manufacturer responsible for batch release

Genzyme Biosurgery ApS
Oliefabriksvej 45
DK - 2770 Kastrup
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products on “restricted” medical prescription, reserved for use in certain specialised areas (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit 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 required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

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 or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

In addition, an updated RMP should be submitted within a year.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall agree the content and the delivery of the Educational Program with the National Competent Authority prior to the launch of MACI in that Member State. The 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 MACI or its components, as well as those involved in follow-up of patients treated with MACI in the Healthcare Establishment, receive the educational pack.

The MAH shall ensure the traceability of each implant by using unique identification numbers assigned to each biopsy (Biopsy ID number), membrane and final MACI product (MAH ID number), as described in the Risk Management Plan.

The educational pack for healthcare professionals shall contain the following components:

- Summary of Product Characteristics
- Educational material on the surgical procedures
- Educational material on appropriate follow-up

The educational material for surgeons and other healthcare professionals involved in the surgical treatment of patients receiving MACI shall include the following key messages:

- Guidance on the selection of suitable patients for MACI treatment and the importance of using MACI only in the approved indication
- The importance of explaining to the patients:
 - The risks associated with the surgical procedures and MACI
 - The need for clinical follow-up
 - The need for rehabilitation following articular cartilage repair
- The need to screen donors using patient questionnaires and laboratory tests for hepatitis C, hepatitis B, HIV and syphilis
- Details on biopsy procurement, and storage and handling of the biopsy harvest
- That MACI is an autologous product and should only be administered to the patient that the biopsy was taken from. Details on the receipt, storage and handling of MACI and its preparation

for implantation, including cross checks of patient details and Biopsy ID and MACI product ID numbers

- Details of the implantation procedure
- Details of appropriate disposal of MACI implant trimmings or unused MACI implants
- Details on how to recognise the signs and symptoms of important identified or potential risks of the product
- Clinical follow up details

The training materials for healthcare professionals involved in the follow-up of patients treated with MACI shall include the following key messages:

- The need for rehabilitation following articular cartilage repair
 - Details on how to recognise the signs and symptoms of important identified or potential risks of the product
 - Details of the rehabilitation program
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- **Obligation to conduct post-authorisation measures**

Not applicable.

Medicinal product no longer authorised

ANNEX III
LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON, OUTER BAG

1. NAME OF THE MEDICINAL PRODUCT

MACI 500,000 - 1,000,000 cells/cm² implantation matrix
Matrix applied characterised autologous cultured chondrocytes

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous chondrocytes on a 14.5 cm² Type I/III collagen membrane, at a density of between 500,000 and 1,000,000 cells per cm²

3. LIST OF EXCIPIENTS

Other ingredients:
Dulbecco's Modified Eagles Medium (DMEM) with 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid sodium (HEPES)

4. PHARMACEUTICAL FORM AND CONTENTS

Implantation matrix.
1 to 2 implantation matrices.

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:

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze. Store below 37°C in the outer carton until ready to use.

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

Any spillage or waste material should be disposed of as surgical waste material in compliance with local practice.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vericel Denmark ApS
Amaliegade 10
DK-1256 Copenhagen K
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/847/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot: {lot number}
Biopsy: {biopsy number}

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 IMMEDIATE PACKAGING UNITS

DISH

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

MACI 500,000 - 1,000,000 cells/cm² implantation matrix

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot: {lot number}

Patient: (name - date of birth {DD.Mmm.YYYY})

Biopsy: {biopsy number}

Matrix: 1/1

Matrix: 1/2

Matrix: 2/2

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 implantation matrix.

6. OTHER

For autologous use only.

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Package leaflet: Information for the user
MACI 500,000 to 1,000,000 cells/cm² for implantation

Matrix applied characterised autologous cultured chondrocytes

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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

1. What MACI is and what it is used for

MACI is used in adults to repair cartilage defects in your knee joint. Cartilage is a tissue that is present in every joint in the body; it protects the ends of bones and allows joints to function smoothly.

MACI is an implant consisting of a porcine derived (derived from pigs) collagen membrane which contains your own cartilage cells (called autologous chondrocytes) and is implanted into your knee. “Autologous” means that your own cells are used which have been taken from your knee (through a biopsy) and grown outside the body.

2. What you need to know before you use MACI

Do NOT use MACI if you:

- are allergic to any of the ingredients of MACI (listed in section 6), or porcine products (derived from pigs), bovine serum (a protein derived from cows) or gentamicin (an antibiotic)
- have severe osteoarthritis of the knee (disease of the joints with pain and swelling)
- currently suffer from inflammatory arthritis or inflammatory joint disease of the knee
- have a known, uncorrected bleeding disorder
- have a growth plate of the knee that is not fully closed.

Warnings and precautions

Your MACI implant has been manufactured specifically for you and cannot be administered to any other patient.

MACI should be implanted in a reasonably healthy joint. This means that other problems in the joint should be corrected before or during MACI implantation.

If you have a sudden occurrence or recent history of **bone or joint infections**, your MACI treatment should be temporarily delayed until your doctor considers that you have recovered.

Tell your doctor or surgeon if you know you have a predisposition for bleeding or poor bleeding control following surgical procedures.

You may also be given antibiotics or pain-killers to help reduce some of the side effects.

It is important that you closely follow the rehabilitation programme recommended by your doctor. Please discuss with your doctor or physical therapist when to re-start specific physical activities.

Your surgeon will give you more information on any special considerations for your particular case.

Other situations in which MACI cannot be given

Even if the surgeon has already taken a small sample of cartilage cells (a biopsy) needed to produce the MACI implant, **it is possible that you will not be eligible for treatment with MACI.**

This is the case if:

- the biopsy is of insufficient quality to produce MACI for you
- the cells cannot be grown in the laboratory
- the increased cells do not meet all the quality requirements.

In such situations, your surgeon will be informed and might have to select an alternative treatment for you.

Older people

The use of MACI is not recommended in patients over 65 years of age who have generalised degeneration of the cartilage or osteoarthritis (disease of the joints with pain and swelling).

Children and adolescents

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

Other medicines and MACI

Please tell your doctor, surgeon or physical therapist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Ask your doctor or surgeon for more information as to which pain medicine you can safely use. Administration of pain relievers into the joint is not recommended.

Pregnancy and breast-feeding

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

MACI is not recommended for pregnant women.

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

Talk to your doctor or surgeon if you are breast-feeding. Depending on your particular situation, your doctor or surgeon will advise you on whether or not to continue breast-feeding.

Driving and using machines

The surgical procedure will have a major impact on your ability to drive and use machines.

Driving 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 MACI

MACI must only be implanted by surgeons who have been specifically trained for this kind of surgery.

A small amount of blood (4 ml) will be taken by a qualified person for testing.

You will need to have **two surgical procedures** to receive this treatment:

1. During the first procedure, a sample of healthy cartilage cells (a biopsy) will be taken from your joint by **arthrotomy** or **arthroscopy**. Your surgeon will explain what arthrotomy and arthroscopy procedures are.

The biopsy will be sent to the cell processing facility. At the cell processing facility, your cartilage cells will be grown aseptically (free from germs) in culture, to increase the number of cells, and placed onto a sterile collagen membrane to make MACI.

2. The final MACI implant will be sent back to your surgeon. The MACI will then be implanted into the cartilage defect in your joint by a second procedure. MACI will be secured in place using a **fibrin sealant**. A fibrin sealant is a type of glue that is made from human blood-clotting proteins.

The length of time between your biopsy and the implantation of MACI can vary depending on the procedure date and the quality and number of cells in the biopsy. On average this will be 6 weeks, however, cells can also be frozen and held in storage for up to 2 years until a convenient date for surgery is agreed between you and your surgeon. Your surgeon will organise the date for implantation.

In rare cases the cell processing facility will not be able to produce MACI from your cells. If this happens, your surgeon will advise you on the best course of action.

Your doctor will discuss with you the specific rehabilitation programme that follows your surgery.

4. Possible side effects

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

When you receive MACI, you may experience side effects soon after the implantation. These effects will gradually reduce over time.

Your doctor may give you other medicines to help reduce any side effects (see section 2 “Warnings and precautions”).

Complications may be related to MACI or to the surgical procedure, or both. Complications related to knee surgery in general may include deep vein thrombosis (blood clotting in a deep vein) and pulmonary embolism (blood clotting in the lung due to blockage of a lung artery). **If you notice any of the following, please contact your doctor immediately**, since these may be symptoms of blood clotting:

- difficulty breathing, chest pain and palpitations
- leg swelling, leg pain and redness

Risks involved with implantation of MACI:

The following **uncommon** side effect may affect up to 1 in 100 people:

- too much cartilage growth.
- the graft may detach completely or partially from the defect in the joint. You may require more surgery to correct this

Risks involved with arthrotomy or arthroscopy or MACI

All surgical procedures carry a certain risk. Your surgeon can explain these to you. The following **rare** side effects may affect up to 1 in 1,000 people:

- infection
- inflammation
- post-operative pain
- bleeding in the joint
- joint stiffness/numbness
- swelling of the joint
- fever

Your surgeon or anaesthetist will explain to you the risks involved with the procedures as well as any additional specific risks that are applicable to you because of your medical history and current medical status.

Reporting of side effects

If you get any side effects, talk to your doctor, surgeon 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 MACI

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

Do not use MACI after the expiry date which is stated on the outer carton and the dish after EXP.

Do not refrigerate or freeze. Store below 37°C in the outer carton until ready to use.

MACI should be used within 6 days after the date of release.

Any spillage or waste material should be disposed as surgical waste material in compliance with local practice.

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 MACI contains

The **active substance** of MACI consists of viable autologous human cartilage cells on a 14.5 cm² Type I/III collagen membrane, at a density of between 0.5 and 1 million cells per cm².

The **other ingredients** are Dulbecco's Modified Eagles Medium (DMEM) with 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid sodium (HEPES).

What MACI looks like and contents of the pack

The implant is an opaque, off-white membrane supplied in 18 ml of colourless solution in a dish.

Marketing Authorisation Holder

Vericel Denmark ApS, Amaliegade 10, DK-1256 Copenhagen K, Denmark

Manufacturer

Genzyme Biosurgery ApS, Oliefabriksvej 51B, DK-2770 Kastrup, Denmark

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

The following information is intended for medical or healthcare professionals only:

During the first procedure a sample of healthy cartilage cells (a biopsy) will be taken from the affected joint by an arthrotomy or arthroscopy.

The biopsy will be sent to the cell processing facility. At the cell processing facility, the cartilage cells will be grown aseptically in culture to expand the number of cells and placed onto a sterile collagen membrane, to make MACI.

MACI will be sent back to the surgeon. At this time MACI will be implanted into the cartilage defect in the affected joint via a second procedure. The MACI implant will be secured in place using a fibrin sealant.

The timing between the removal of the biopsy and the implantation of the MACI implant can vary depending on logistics and the quality and number of cells in the biopsy. On average this will be 6 weeks, however, cells can also be cryopreserved and held in storage for up to 2 years until a convenient date for surgery is agreed between the patient and surgeon.

The surgeon will organise the date for implantation in consultation with the Marketing Authorisation Holder (MAH) or its local representative. In rare cases the MAH will not be able to produce a MACI implant from the available cells. If this occurs the surgeon will advise the patient on the best course of action.

Please consult the Surgical Technique Manual for further information.