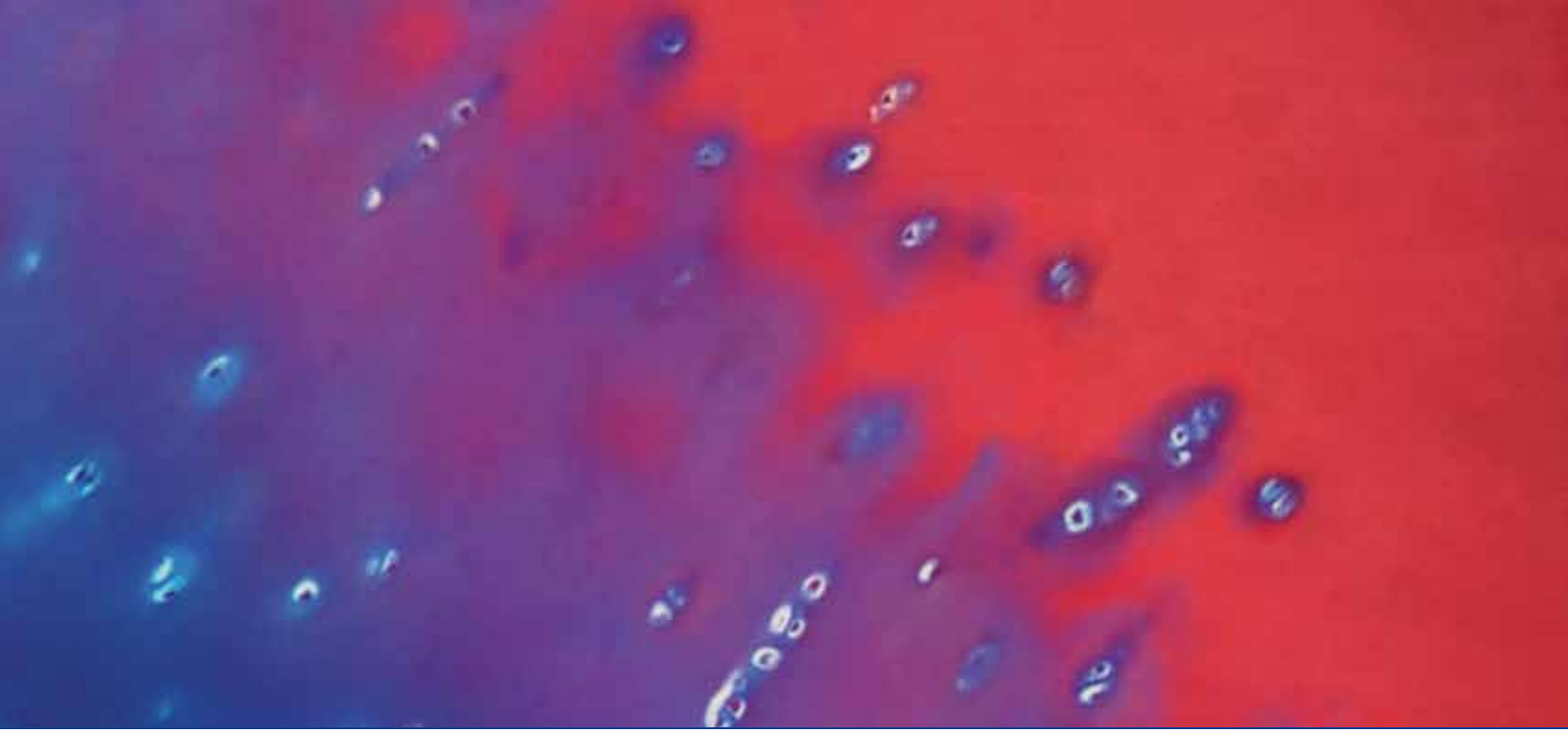

REHABILITATION GUIDELINES

Autologous Chondrocyte Implantation using Carticel (autologous cultured chondrocytes)

Michael M. Reinold, PT, ATC*
Kevin E. Wilk, PT*
Jeffrey R. Dugas, MD*
E. Lyle Cain, MD*
Scott D. Gillogly, MD*

**These individuals were working as consultants on behalf of the manufacturer.*

Carticel®
(autologous cultured chondrocytes)

Indication

Carticel® (autologous cultured chondrocytes) is an autologous cellular product indicated for the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral or trochlea), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft).

Carticel should only be used in conjunction with debridement, placement of a periosteal flap and rehabilitation. The independent contributions of the autologous cultured chondrocytes and other components of the therapy to outcome are unknown.

Carticel is not indicated for the treatment of cartilage damage associated with generalized osteoarthritis.

Carticel is not recommended for patients with total meniscectomy unless surgically reconstructed prior to or concurrent with Carticel implantation.

Important Safety Information

Do not use in patients with a known history of hypersensitivity to gentamicin, other aminoglycosides or materials of bovine origin.

The occurrence of subsequent surgical procedures (SSPs), primarily arthroscopy, following Carticel implantation is common. In the Study of the Treatment of Articular Repair (STAR), forty-nine percent (49%) of patients underwent an SSP on the treated knee, irrespective of their relationship to Carticel, during the 4-year follow up.

Carticel is not routinely tested for transmissible infectious diseases and may transmit disease to the healthcare provider handling Carticel.

Pre-existing conditions, including meniscal tears, joint instability, or malalignment should be assessed and treated prior to or concurrent with Carticel implantation.

It should not be used in patients who have previously had cancer in the bones, cartilage, fat or muscle of the treated limb.

The most common serious adverse events (≥5% of patients), derived from STAR, include arthrofibrosis/joint adhesions, graft overgrowth, chondromalacia or chondrosis, cartilage injury, graft complication, meniscal lesion and graft delamination.

Use of Carticel in children, patients over age 65, or in joints other than the knee has not yet been assessed.

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Please see Important Safety Information for Carticel on page 2 and on back cover.

The following has been provided as general guidelines for rehabilitation following autologous cultured chondrocyte implantation. This is intended for use by physical therapists. Individual results may vary. The emphasis of this guideline is to protect the graft site and return the patient to an optimal level of function. Notwithstanding the foregoing, the information provided in this document is intended for educational purposes. It is not a substitute for medical care nor should it be construed as medical advice or product labeling. Consultation with the patient's treating surgeon or orthopedist is recommended prior to implementing a rehabilitation program.

Encourage patient adherence to the prescribed rehabilitation program. This is important and deviation from the program may compromise clinical benefit from Carticel® (autologous cultured chondrocytes).

Lesion size, location and patient age are significant factors in determining a rehabilitation program for each patient.

Although times frames have been established, it is more important that goals are reached at the end of each phase prior to progression to the next. Patients may return to various sports activities as progression in rehabilitation and cartilage healing allows.

It is important to avoid excessive loading / weight bearing on the graft site to ensure proper healing. Take note of specific precautions mentioned in the guidelines. Information regarding the location, size, and specifics of the implantation site should be obtained from the surgeon.

Pain and swelling need to be carefully monitored throughout the rehabilitation process. If either occur, the triggering activity needs to be identified and appropriately adjusted to lessen the irritation. Ice packs maybe used to control swelling. Ignoring these symptoms may compromise the success of the surgery and the patient's outcome.

At anytime during the rehabilitation process or after, if sharp pain with locking or swelling is experienced,the patient's physician should be notified as soon as possible.

Introduction

Articular cartilage defects of the knee are a common cause of pain and functional disability in the orthopedics and sports medicine practice. The avascular nature of articular cartilage predisposes the individual to progressive symptoms and degeneration due to the inability of articular cartilage to heal. These guidelines provide specific recommendations for optimal rehabilitation following implantation with Carticel.

These suggested programs are designed using knowledge of basic science, anatomy, and biomechanics of articular cartilage as well as the natural course of healing following implantation and are not intended as a substitute for individual clinical judgement. The goal is to achieve the best possible functioning in each patient as quickly and safely as possible.

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Contents

Vericel would like to acknowledge and thank Lisa Giannone, PT for her contributions in developing the original Carticel rehabilitation protocol, on which these protocols are based.

Specific Rehabilitation **GUIDELINES**

One of the most important principles involved in rehabilitation following Carticel implantation is program individualization. Each patient will have a unique response to the surgical procedure and will therefore progress through rehabilitation at a different pace. Specific factors including lesion size and location, tissue quality, age, lifestyle, and general health will affect the patient's postoperative response. Therefore, these rehabilitation guidelines are designed to provide a general framework for exercise progression that will help return the patient to functional activities in a safe manner. Some patients may progress more rapidly, advancing range of motion and weight bearing status in a controlled fashion. The rehabilitation specialist should monitor joint line pain, effusion, and symptomatic complaints to determine if the patient is progressing appropriately. However, the rehabilitation program should continue to avoid deleterious forces to the graft site, including excessive compressive and shear forces, during exercise progression.

Rehabilitation varies per person based on age, weight, tissue quality, motivation, and activity level prior to surgery. Target timeframes noted in each phase are approximate and should be adjusted to the individual progress of each patient. Each person is different; rehabilitation progression is based on the size, location, quantity, containment, and nature® of the defect, as well as mental attitude.

The following section provides the rehabilitation guidelines for isolated femoral condyle and trochlea lesions[1]. There are four distinct phases based on the healing process following the implantation of Carticel. Certain criteria must be achieved prior to the patient progressing to each phase of the program. Specific goals and criteria to progress are listed under each phase. There is a great deal of variability from patient to patient. When a patient achieves the goals of a particular rehabilitation phase, he or she may be moved to the next phase at the surgeon's discretion.

Exercises are progressed based on the patient's subjective reports of symptoms, and the clinical assessment of swelling and crepitation. If pain or swelling occurs with any activities, they must be modified to decrease symptoms, and the orthopedic surgeon should be contacted.

Please see the VARIATIONS section (pages 16-18) for a discussion of recommended alterations to the basic rehabilitation guidelines that address concomitant procedures.

Carticel Implantation

Femoral Condyle Rehabilitation Guidelines[1]

(Intended for small lesions [<5cm^2] with no concomitant procedure)

For concomitant procedures, large lesions (≥5cm^2), OCD, uncontained or multiple lesions, please see additional considerations in the Rehabilitation Guideline Variations section starting on page 16.

PHASE I - PROTECTION PHASE (WEEKS 0-6)

Goals:

- Protect healing tissue from load and shear forces
- Decrease pain and effusion
- Gradually improve knee flexion
- Restore full passive knee extension
- Regain quadriceps control

Brace:

- Locked at 0˚ during weight-bearing activities
- Sleep in locked brace for 2-4 weeks

Weight-Bearing:

- Non-weight-bearing for first week, may begin toe-touch weight bearing immediately per physician instructions
- Toe touch weight-bearing (approx. 20-30 lbs) weeks 2-3
- Partial weight-bearing (approx. 1/4 body weight) at weeks 4-5

Range of Motion:

- Motion exercise 6-8 hours post-operative
- Full passive knee extension immediately
- Initiate Continuous Passive Motion (CPM) day 1 for total of 6 hours/day (0˚-40˚) for 2-3 weeks
- Progress CPM range of Motion (ROM) as tolerated 5˚-10˚ per day
- May continue CPM for total of 6-8 hours per day for up to 6 weeks
- Patellar mobilization (4-6 times per day)
- Motion exercises throughout the day
- Passive knee flexion ROM 2-3 times daily
- Knee flexion ROM goal is 90˚ by 1-2 weeks
- Knee flexion ROM goal is 105˚ by 3-4 weeks and 120˚ by week 5-6
- Stretch hamstrings and calf

Strengthening Program:

- Ankle pump using rubber tubing
- Quad setting
- Multi-angle isometrics (co-contractions Q/H)
- Active knee extension 90˚-40˚ (no resistance)
- Straight leg raises (4 directions)
- Stationary bicycle when ROM allows
- Biofeedback and electrical muscle stimulation, as needed
- Isometric leg press by week 4 (multi-angle)
- May begin use of pool for gait training and exercises by week 4

Functional Activities:

- Gradual return to daily activities
- If symptoms occur, reduce activities to reduce pain and inflammation
- Extended standing should be avoided

Carticel Implantation

Femoral Condyle Rehabilitation Guidelines[1] continued

Swelling Control:

- Ice, elevation, compression, and edema modalities as needed to decrease swelling

Brace:

- Locked at 0˚ during weight-bearing activities
- Sleep in locked brace for 2-4 weeks

Criteria to Progress To Phase II:

- Full passive knee extension
- Knee flexion to 120˚
- Minimal pain and swelling
- Voluntary quadriceps activity

PHASE II - TRANSITION PHASE (WEEKS 6-12)

Goals:

- Gradually increase ROM
- Gradually improve quadriceps strength/endurance
- Gradual increase in functional activities

Brace:

- Discontinue post-operative brace by week 6
- Consider unloading knee brace

Weight-Bearing:

- Progress weight-bearing as tolerated
- Progress to full weight-bearing by 8-9 weeks
- Discontinue crutches by 6 weeks

Range of Motion:

- Gradual increase in ROM
- Maintain full passive knee extension
- Progress knee flexion to 125˚-135˚ by week 8
- Continue patellar mobilization and soft tissue mobilization, as needed
- Continue stretching program

Strengthening Program:

- Initiate weight shifts week 6
- Initiate mini-squats 0˚-45˚ by week 8
- Closed kinetic chain exercises (leg press)
- Toe-calf raises by week 8
- Open kinetic chain knee extension progress 1 lb/week
- Stationary bicycle, low resistance (gradually increase time)
- Treadmill walking program by weeks 10-12
- Balance and proprioception drills
- Initiate front and lateral step-ups and wall squats by weeks 8-10
- Continue use of biofeedback and electrical muscle stimulation, as needed
- Continue use of pool for gait training and exercise

Functional Activities:

- As pain and swelling (symptoms) diminish, the patient may gradually increase functional activities
- Gradually increase standing and walking

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Carticel Implantation

Femoral Condyle Rehabilitation Guidelines[1] continued

Criteria to Progress to Phase III:

- Full range of motion
- Acceptable strength level
  - Hamstrings within 20% of contralateral leg
  - Quadriceps within 30% of contralateral leg
- Balance testing within 30% of contralateral leg
- Able to walk 1-2 miles or bike for 30 minutes

PHASE III - MATURATION PHASE (WEEKS 12-26)

Goals:

- Improve muscular strength and endurance
- Increase functional activities

Range of Motion:

- Patient should exhibit 125˚-135˚ flexion

Exercise Program:

- Leg press (0˚-90˚)
- Bilateral squats (0˚-60˚)
- Unilateral step-ups progressing from 2” to 8”
- Forward lunges
- Walking program
- Open kinetic chain knee extension (0˚-90˚)
- Bicycle
- Stair machine
- Swimming
- Ski machine/elliptical trainer

Functional Activities:

- As patient improves, increase walking (distance, cadence, incline, etc.)

Maintenance Program:

- Initiate by weeks 16-20
- Bicycle – low resistance, increase time
- Progressive walking program
- Pool exercises for entire lower extremity
- Straight leg raises
- Leg press
- Wall squats
- Hip abduction / adduction
- Front lunges
- Step-ups
- Stretch quadriceps, hamstrings, calf

Criteria to Progress to Phase IV:

- Full non-painful ROM
- Strength within 80%-90% of contralateral extremity
- Balance and/or stability within 75%-80% of contralateral extremity
- Rehabilitation of functional activities causes no or minimal pain, inflammation or swelling

Carticel Implantation

Femoral Condyle Rehabilitation Guidelines[1] continued

PHASE IV - FUNCTIONAL ACTIVITIES PHASE (WEEKS 26-52)

Goals:

- Gradual return to full unrestricted functional activities

Exercises:

- Continue maintenance program progression 3-4 times/ week
- Progress resistance as tolerated
- Emphasis on entire lower extremity strength and flexibility
- Progress agility and balance drills
- Impact loading program should be specialized to the patient's demands
- Progress sport programs depending on patient variables

Functional Activities:

- Patient may return to various sport activities as progression in rehabilitation and cartilage healing allows. Generally, low-impact sports such as swimming, skating, in-line skating, and cycling are permitted at about 6 months. High impact sports such as jogging, running, and aerobics may be performed at 8-9 months for small lesions or 9-12 months for larger lesions. High impact pivoting sports such as tennis, basketball, football, and baseball may be allowed at 12-18 months. Individual results may vary. Many patients are able to participate in sports with some limitations.

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Carticel Implantation

Trochlea Rehabilitation Guidelines[1]

(Intended for small lesions [<5cm^2] with no concomitant procedure)

For concomitant procedures, large lesions (≥5cm^2), OCD, uncontained or multiple lesions, please see additional considerations in the Rehabilitation Guideline Variations section starting on page 16.

PHASE I - PROTECTION PHASE (WEEKS 0-6)

Goals:

- Protect healing tissue from load and shear forces
- Restore full passive knee extension
- Regain quadriceps control
- Decrease pain and effusion

Brace:

- Locked at 0˚ during ambulation and weight-bearing activities
- Sleep in locked brace for 2-4 weeks

Weight-Bearing:

- Immediate partial weight-bearing in full extension, as tolerated
- 25% body weight with brace locked
- 50% body weight by week 2 in brace
- 75% body weight by weeks 3-4 in brace

Range of Motion:

- Immediate motion exercise days 1-2
- Full passive knee extension immediately
- Initiate CPM on day 1 for total of 8-12 hours/day (0˚-60˚; if lesion > 6 cm^2 0˚-40˚) for first 2-3 weeks
- Progress CPM ROM as tolerated 5˚-10˚ per day
- May continue use of CPM for total of 6-8 hours per day for 6 weeks
- Patellar mobilization (4-6 times per day)
- Motion exercises throughout the day
- Passive knee flexion ROM 2-3 times daily
- Knee flexion ROM goal is 90˚ by 2-3 weeks
- Knee flexion ROM goal is 105˚ by 3-4 weeks, and 120˚ by week 6
- Stretch hamstrings, calf

Strengthening Program:

- Ankle pump using rubber tubing
- Quad setting
- Straight leg raises (4 directions)
- Toe-calf raises by week 2
- Stationary bicycle when ROM allows
- Biofeedback and electrical muscle stimulation, as needed
- Isometric leg press by week 4 (multi-angle)
- Initiate weight shifts by week 4
- May begin pool therapy for gait training and exercise by week 4

Functional Activities:

- Gradual return to daily activities
- If symptoms occur, reduce activities to reduce pain and inflammation
- Extended standing should be avoided
- Use caution with stair climbing

Swelling Control:

- Ice, elevation, compression, and edema modalities as needed to decrease swelling

Criteria to Progress to Phase II:

- Full passive knee extension
- Knee flexion to 115˚–120˚
- Minimal pain and swelling
- Voluntary quadriceps activity

Carticel Implantation

Trochlea Rehabilitation Guidelines[1] continued

PHASE II - TRANSITION PHASE (WEEKS 6-12)

Goals:

- Gradually increase ROM
- Gradually improve quadriceps strength/endurance
- Gradually increase functional activities

Brace:

- Discontinue brace by 6 weeks

Weight-Bearing:

- Progress weight-bearing as tolerated
- Progress to full weight-bearing by 6-8 weeks
- Discontinue crutches by 6-8 weeks

Range of Motion:

- Gradually increase ROM
- Maintain full passive knee extension
- Progress knee flexion to 120˚-125˚ by week 8
- Continue patellar mobilization and soft tissue mobilization, as needed
- Continue stretching program

Strengthening Exercises:

- Closed kinetic chain exercises (leg press 0˚-60˚) by week 8
- Initiate mini-squats 0˚-45˚ by week 8
- Toe-calf raises at week 6
- Open kinetic chain knee extension without resistance
- Begin knee extension 0˚-30˚ then progress to deeper angles
- Stationary bicycle (gradually increase time)
- Stair machine by week 12
- Balance and proprioception drills
- Initiate front and lateral step-ups by weeks 8-10
- Continue use of biofeedback and electrical muscle stimulation, as needed

Functional Activities:

- As pain and swelling (symptoms) diminish, the patient may gradually increase functional activities
- Gradually increase standing and walking

Criteria to Progress to Phase III:

- Full range of motion
- Acceptable strength level
  - Hamstrings within 20% of contralateral leg
  - Quadriceps within 30% of contralateral leg
- Balance testing within 30% of contralateral leg
- Able to walk 1-2 miles or bike for 30 minutes

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Carticel Implantation
Trochlea Rehabilitation Guidelines[1] continued

PHASE III - REMODELING PHASE (WEEKS 12-32)

Goals:

- Improve muscular strength and endurance
- Increase functional activities

Range of Motion:

- Patient should exhibit 125˚-135˚ flexion

Exercise Program:

- Leg press (0˚-60˚; progress to 0˚-90˚)
- Bilateral squats (0˚-60˚)
- Unilateral step-ups progressing from 2" to 6"
- Forward lunges
- Walking program on treadmill
- Open kinetic chain knee extension (90˚-40˚) – progress 1 lb every 2 weeks beginning
- Week 20 if no pain or crepitation – must monitor symptoms
- Bicycle
- Stair machine
- Swimming
- Ski machine/elliptical trainer

Functional Activities:

- As patient improves, you may increase walking (distance, cadence, incline, etc.)
- Light running can be initiated toward end of phase based on physician evaluation

Maintenance Program:

- Initiate by weeks 16-20
- Bicycle – low resistance, increase time
- Progressive walking program
- Pool exercises for entire lower extremity
- Straight leg raises
- Leg press
- Wall squats
- Hip abduction / adduction
- Front lunges
- Step-ups
- Stretch quadriceps, hamstrings, calf

Criteria to Progress to Phase IV:

- Full non-painful ROM
- Strength within 80%-90% of contralateral extremity
- Balance and/or stability within 75%-80% of contralateral extremity
- Rehabilitation of functional activities causes no or minimal pain, inflammation or swelling

Carticel Implantation

Trochlea Rehabilitation Guidelines[1] continued

PHASE IV - MATURATION PHASE (8-15 MONTHS)

Goals:

- Gradually return to full unrestricted functional activities

Exercises:

- Continue maintenance program progression 3-4 times/week
- Progress resistance as tolerated
- Emphasis on entire lower extremity strength & flexibility
- Progress agility and balance drills
- Progress walking program as tolerated
- Impact loading program should be specialized to the patient's demands
- No jumping or plyometric exercise until 12 months
- Progress sport programs depending on patient variables

Functional Activities:

- Patient may return to various sport activities as progression in rehabilitation and cartilage healing allows. Generally, low-impact sports such as swimming, skating, in-line skating, and cycling are permitted at about 6 months. High impact sports such as jogging, running, and aerobics may be performed at 8-9 months for small lesions or 9-12 months for larger lesions. High impact pivoting sports such as tennis, basketball, football, and baseball may be allowed at 12-18 months. Individual results may vary. Many patients are able to participate in sports with some limitations.

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Notes:

Rehabilitation Guideline VARIATIONS[1]

Additional surgical procedures to address patellofemoral and tibiofemoral alignment, ligamentous laxity, and meniscal pathology are often performed at the time of the Carticel implantation to minimize possible contributing factors to graft failure due to excessive compressive and shear forces. Rehabilitation programs for Carticel may often require alterations based on the unique presentation of each patient. The next section will briefly discuss variations to the isolated guidelines previously discussed based on the extent of lesion damage and concomitant procedures performed.

Anterior Cruciate Ligament Reconstruction

Reconstruction of the anterior cruciate ligament (ACL) using an ipsilateral patellar tendon graft generally requires an increased rate of passive range of motion (ROM) restoration. Harvesting the ipsilateral patellar tendon may predispose the patient to the development of arthrofibrosis and loss of motion due to excessive scar tissue formation in the anterior aspect of the knee. Emphasis is placed on full passive knee extension and patellar mobilization immediately following surgery. Passive ROM is slightly accelerated for a femoral condyle implantation during the initial phase of rehabilitation with the goals of:

- 90˚ of passive knee flexion by week 1
- 100˚-105˚ by week 2
- 115˚ by week 4
- 125˚ by week 6
- 135˚ by week 8.

Weight-bearing precautions and exercise progression are similar to the isolated femoral condyle guideline. Lesions on the trochlea with a concomitant ACL reconstruction require a more conservative approach than condyle lesions. Passive ROM is progressed slowly at first from:

- 45˚ by day 3
- 60˚-75˚ by day 7
- 90˚ by day 10
- 100˚ by day 14
- 105˚ by week 3
- 115˚ by week 4
- 125˚ by week 6

Partial weight bearing is typically performed immediately in a brace locked in extension similar to an isolated trochlea lesion.

The use of a hamstring autogenous graft for ACL reconstruction involves similar guidelines as the patellar tendon graft. However, caution should be taken with overaggressive hamstring strengthening in the early postoperative phases to minimize graft site morbidity. Aggressive strengthening of the hamstrings should typically be avoided for the first 6-8 weeks.

Allograft tissue may also be used for ACL reconstruction. Rehabilitation does not differ significantly from an autogenous graft although the patient may feel less anterior knee pain due to minimized graft morbidity.

Meniscal Allograft

Meniscal allograft transplantation alters the rehabilitation program significantly to allow healing of the meniscus postoperatively. While weight bearing guidelines are similar to that of the isolated femoral condyle guidelines, ROM and exercise progression is altered. The rate of passive ROM restoration is slightly decelerated to protect the meniscus with the goals of:

- 60˚ of knee flexion by week 1
- 90˚ by week 2
- 100˚ by week 5
- 110˚ by week 6
- 120˚ by week 7
- 125˚ by week 8

No active knee flexion past 90˚ should be allowed for the first 6-8 weeks to minimize strain on the meniscus due to the close

anatomical relationship of the hamstrings, capsular tissue, and meniscus. Furthermore, resisted hamstring strengthening is typically avoided until week 12. The use of bicycle and pool therapy usually begins by week 6-8.

Distal Realignment

A distal realignment, involving an anteromedialization of the tibial tubercle, is often performed during trochlea implantations. Several aspects of the rehabilitation program should be altered to avoid excessive strain on the tibial tubercle. Passive ROM should be progressed slowly with the goals of:

- 45˚ by day 5
- 60˚ by the end of week 1
- 75˚ by week 3, 90˚ by week 4
- 115˚ by week 5
- 125˚ by week 6
- 125˚-135˚ by week 8

Weight-bearing progression is similar to that of the isolated trochlea guidelines with immediate partial weight bearing with a knee brace locked in full extension. Scar tissue management and patellar mobilization are recommended to be performed to minimize the formation of adhesions. Open kinetic chain knee extensions can be initiated without resistance from 60˚-0˚ by weeks 6-8 as tolerated. The use of a bicycle and pool therapy can be initiated by weeks 6-8.

High Tibial Osteotomy

A high tibial osteotomy to realign the tibiofemoral joint generally requires a slightly accelerated passive ROM progression to avoid motion loss postoperatively with the goals of:

- 90˚ of knee flexion by week 1
- 105˚ by week 2, 115˚ by week 3
- 125˚ by week 4
- A gradual progression past 125˚ beginning by week 6

Weight-bearing progression is similar to that of the isolated femoral condyle lesion, although weight-bearing may be delayed based on radiographic evidence of bone formation, if bone grafting is used, lesion size or location. Emphasis should be placed on restoring strength and flexibility of the quadriceps for optimal joint function. Furthermore, the use of external devices to alter the applied load of the tibiofemoral joint may be used such as orthotics, insoles, and heel wedges. The use of an osteoarthritis unloading brace is recommended when the postoperative knee brace is discharged by weeks 6-8.

Lesion Size

The rehabilitation program may also vary based on the size of the lesion due to a larger area of articulation during weight bearing and exercises. The exact variation will differ based on the location of the lesion, although a larger lesion is generally considered to be 4cm^2 or greater.

Larger lesions on the femoral condyles will generally necessitate a slower weight-bearing progression, particularly for the medial femoral condyle in the varus-aligned knee. Typically, weight-bearing progression is delayed 2-4 weeks. Full weight bearing without the use of crutches is progressed to by weeks 10-12, and may be longer for more complicated lesions. The use of an unloader brace is recommended to decrease compressive forces to the graft site.

Conversely, large lesions on the trochlea may still progress with the same weight-bearing guidelines as smaller lesions. However, range of motion may be slightly delayed to minimize shear forces on the patellofemoral cartilage. Knee flexion passive range of motion should be progressed based on a patient's report of pain or symptoms. In general, ROM is performed from:

- 0˚- 45˚ during the first week
- Progressing to 75˚ by week 2
- 90˚ by week 3
- 100˚-105˚ by week 4
- Progressing to 120˚ by weeks 6-8

Open kinetic chain active knee extension exercises should also be avoided for large trochlea lesions until week 10 and are then progressed slowly with low resistance. Aggressive resisted knee extension exercises should be avoided for 9-12 months.

Uncontained Lesion

Large lesions are often uncontained lesions. The presence of an uncontained lesion will alter the weight bearing progression due to the complexity of the repair and the stability of the suture fixation. The rehabilitation program should be altered similar to the guidelines for large condyle or trochlea lesions. Therefore, for uncontained condyle lesions, the weight-bearing progression is typically delayed approximately 2-4 weeks, and for uncontained trochlea lesions the range of motion and exercise programs are decelerated similar to large lesions. Heavy resisted open kinetic chain exercises should be avoided for at least 3-6 months postoperatively on the femur and 9-12 months on the trochlea. The rehabilitation progression will be highly individualized for these patients based on the physician's discretion and the size and containment of the lesion.

Osteochondritis Dissecans

The rehabilitation program following a Carticel® (autologous cultured chondrocytes) implantation procedure to address an osteochondritis dissecans does not vary considerably in terms of immediate postoperative weight bearing, range of motion, or exercises guidelines. However, when the patient begins returning to functional activities during the later phases of rehabilitation, a slower approach is typically utilized. A return to low impact activities is usually delayed for at least 6 months postoperative. Emphasis should be placed on a gradual program of:

- Walking by 6-8 months
- Progressing to light jogging and running by 8-9 months
- Eventually jumping by 9-12 months postoperative at the earliest

In the event that a bone grafting procedure is needed concomitantly, the patient should be non-weight bearing for approximately 2-4 weeks, progressing to full weight bearing by 12-16 weeks.

Multiple Lesions

The presence of multiple lesions will alter the rehabilitation program based on the location of each lesion, and will typically involve a more conservative postoperative program. For multiple lesions on the femoral condyles or trochlea, the rehabilitation program is adjusted similar to the guidelines for a large condylar or trochlea lesion, respectively. However, the combination of a lesion on the condyle as well as the trochlea will vary significantly. The rehabilitation program should take into consideration the precautions of both lesion sites. Therefore, the weight-bearing progression would typically assume the postoperative precautions similar to an isolated femoral condyle lesion to avoid overaggressive compressive forces. Conversely, the range of motion and exercise progression would typically assume the postoperative precautions similar to a trochlea lesion to avoid detrimental shear forces. Thus the patient should be non-weight bearing for:

- 2 weeks postoperative
- Progressing to 25% body weight by week 5
- 50% body weight by week 6
- Gradually progressing to full weight bearing by weeks 9-12 based on lesion specifics
- Knee flexion range of motion should progress to:
  - 90˚ by week 3
  - 105˚ by week 4
  - 120˚ by week 6

Lesion size may further delay the range of motion and weight-bearing progression.

Notes:

PRINCIPLES of Rehabilitation Following **Carticel** Implantation

There are several key principles involved when designing rehabilitation programs following Carticel implantation. These key principles include: creating a healing environment, the biomechanics of the knee, restoring soft tissue balance, reducing post-operative pain, restoring muscle function, gradually progressing applied loads, and team communication. We briefly describe each one as they relate to the rehabilitation program.

Create a Healing Environment

The first principle of rehabilitation following Carticel implantation involves creating an environment that facilitates the repair process while avoiding potentially deleterious forces to the graft site. This involves a thorough knowledge of the physiological repair process following implantation. Through animal studies, as well as the close monitoring of the maturation of the repair tissue in human patients via arthroscopic examination, four different biological phases of maturation have been identified.[2-6]

The first biologic phase is the proliferation phase, which usually involves the first six weeks following cell implantation. During the first 24 hours after cell implantation, the cells line the base of the lesion, proliferate and produce a matrix that will fill the defect with a soft repair tissue up to the level of the periosteal cover. Passive range of motion and controlled partial weight bearing will help promote cell function. During this initial phase, controlled active and passive range of motion and a gradual weight-bearing progression are critical components to the rehabilitation process.

Controlled compression and decompression forces observed during weight bearing may provide the signals to the chondrocytes to produce an appropriate matrix. A progression of partial weight bearing with crutches is used to gradually increase the amount of load applied to the weight-bearing surfaces of the joint. The use of a pool or aquatic therapy may be beneficial to begin gait training and lower extremity exercises. The buoyancy of the water decreases the amount of weight-bearing forces to approximately 25% body weight with a water depth to the axilla, and 50% with water depth to the waist.[7] Thus a pool may be used during early phases of rehabilitation to perform limited weight-bearing activities.

Passive range of motion activities, such as continuous passive motion (CPM) machines, are also generally performed beginning as early as 6-8 hours after surgery to nourish the healing articular cartilage and prevent the formation of adhesions. CPM usage is typically performed for at least 6 to 8 weeks, with recommended usage for approximately 6 to 8 hours per day, which may be broken into 2-3 hour segments. Motion exercises may assist in creating a smooth, low frictional surface by sliding against the joint's articular surface. The use of CPM has been shown to enhance cartilage healing and long-term outcomes following articular cartilage procedures.[8,9]

The second biologic phase of maturation is the transitional phase, which typically includes weeks 7 through 12. The repair tissue at this point is spongy and compressible with little resistance. Upon arthroscopic examination, the tissue may, in fact, have a wave-like motion to it when sliding a probe over the tissue. During this phase, the patient usually progresses from partial weight bearing to full weight bearing. Continued maturation of the repair tissue is fostered through higher level functional and motion exercises. It is during this phase that patients typically resume most normal activities of daily living.

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The third biologic phase of maturation is known as the remodeling phase, and typically occurs from 12 weeks through 32 weeks postoperatively. During this phase there is usually a continuous production of matrix with further remodeling into a more organized structural tissue. The tissue at this point has the consistency of soft plastic upon probing. As the tissue becomes more firm and integrated, it allows for more functional training activities to be performed. At this point, the patient typically notes improvement of symptoms and has generally normal motion.

The final biologic phase is known as the maturation and optimization phase, which can last for 15 up to 18 months post-implantation, depending upon the size and location of the lesion. It is during this phase that the repair tissue usually reaches its full maturation. The stiffness of the cartilage resembles that of the surrounding tissue.[5,6]

Biomechanics of the Knee

The next rehabilitation principle involves the biomechanics of the tibiofemoral and patellofemoral joint during normal joint articulation.

Articulation between the femoral condyle and tibial plateaus is constant throughout knee range of motion. The anterior surface of the femoral condyles is in articulation with the middle aspect of the tibial plateau near full knee extension. As the knee moves into greater degrees of knee flexion, the femoral condyles progressively roll and slide posteriorly, causing articulation to shift posteriorly on the femoral condyle and tibial plateaus.[10, 11]

Articulation between the inferior margin of the patella and the trochlea begins at approximately 10° - 20° of knee flexion.[11] As the knee proceeds into greater degrees of knee flexion, the contact area of the patellofemoral joint moves proximally along the patella. At 30°, the area of patellofemoral contact is approximately $2cm^2$.[11] The area of contact gradually increases as the knee is flexed. At 90° of knee flexion, contact area increases up to approximately $6cm^2$.[12]

Using this knowledge of the joint kinematics, the rate of weight bearing and passive range of motion may be progressed based on the exact location of the lesion. For example, a lesion on the anterior aspect of the femoral condyle may be progressed into deeper degrees of passive knee flexion without causing articulation at the graft site. Conversely, lesions on the posterior condyle may require a slower rate of passive range of motion progression due to the progressive rolling and sliding component of articulation during deeper flexion. Furthermore, lesions on a non-weight-bearing surface, such as the trochlea, may include immediate partial weight bearing with a brace locked in full knee extension without causing excessive compression on the graft site. The use of a postoperative brace is recommended to assure that weight bearing is performed in a non-articulating range of motion.

Rehabilitation exercises can be altered based on the biomechanics of the knee to avoid excessive compressive or shearing forces. Open kinetic exercises, such as knee extension, are commonly performed from 90˚ - 40˚ of knee flexion. This range of motion provides the lowest amount of patellofemoral joint reaction forces while exhibiting the greatest amount of patellofemoral contact area.[11- 14] Closed kinetic chain exercises, such as the leg press, vertical squats, lateral step-ups, and wall squats, are best performed initially from 0˚ to 30˚ and then progressed to 0˚ to 60˚ where tibiofemoral and patellofemoral joint reaction forces are lowered.[11-14] As the graft site heals and patient symptoms subside, the ranges of motion should be progressed to allow greater muscle strengthening in larger ranges. Exercises are progressed based on the patient's subjective reports of symptoms, and the clinical assessment of swelling and crepitation. If pain or swelling occurs with any activities, they must be modified to decrease symptoms, and the orthopedic surgeons should be contacted.

PRINCIPLES of Rehabilitation Following **Carticel** Implantation

Restore Soft Tissue Balance

One of the more important aspects of rehabilitation following Carticel implantation, involves the avoidance of arthrofibrosis. This is usually achieved by focusing on the restoration of full knee extension, patella mobility, and soft tissue flexibility of the knee and entire lower extremity. The inability to fully extend the knee may result in abnormal joint kinematics and subsequent increases in patellofemoral and tibiofemoral joint contact pressure, strain on the quadriceps muscle, and muscular fatigue.[15] Several authors have reported that immediate(post-operative day 1) motion is essential to avoid range of motion complications and minimize poor functional outcomes.[16, 17] Therefore, a drop-lock post-operative knee brace locked into 0˚ of extension is generally used, and CPM and passive range of motion out of the brace are typically performed 6-8 hours following surgery.

The goal is to achieve at least 0˚ of knee extension the first few days post-operatively. Specific exercises utilized may include manual passive range of motion exercises performed by the rehabilitation specialist, supine hamstring stretches with a wedge under the heel, and gastrocnemius stretching with a towel. Overpressure of 6-12 pounds may be used for a low-load, long-duration stretch as needed to achieve full extension.

Patients will often exhibit a certain amount of hyperextension preoperatively or in the uninvolved knee. For patients with significant hyperextension of the uninvolved extremity, regaining approximately 5°-7° of hyperextension through stretching techniques in the clinic is suggested. The remaining hyperextension may be achieved through functional activities. We believe this allows the patient to gain a greater degree of neuromuscular control at the end range of extension, and avoids uncontrolled and unexpected hyperextension movements.

The loss of patellar mobility following Carticel implantation may be due to various reasons, including excessive scar tissue adhesions along the medial and lateral gutters. The loss of patellar mobility may result in range of motion complications and difficulty recruiting quadriceps contraction. Patellar mobilization in the medial-lateral and superior-inferior directions can be performed by the rehabilitation specialist and independently by the patient during their home exercise program.

Soft tissue flexibility and pliability are also important for the entire lower extremity. Soft tissue massage and scar management can be performed to prevent adhesion development around the anterior, medial, and lateral aspects of the knee. In addition, flexibility exercises can be performed for the entire lower extremity, including the hamstrings, hip, and calf musculature.

Post-operative adhesion formation may result in range of motion complications. The most beneficial treatment for arthrofibrosis is prevention. Early emphasis on extension and flexion range of motion, patella mobilization, and continuous passive range of motion at home is important to help prevent arthrofibrosis. It is essential that the patient achieve full knee extension immediately following surgery. This may be facilitated through the use of passive extension range of motion, hamstring stretching, and gastrocnemius stretching. In the event that the patient develops flexion or extension range of motion complications, the rehabilitation specialist may perform several therapeutic techniques. These can include moist heat, ultrasound to the anterior knee, scar and soft tissue mobilization, patellar mobilization, and passive range of motion and flexibility exercises. Low-load, long-duration stretches to achieve full knee extension may also be performed in the supine position, incorporating a wedge underneath the patients heel and concomitant weight (ranging from 5-12 pounds) applied to the distal thigh, typically for 10-12 minutes. It is possible for adhesions to form and attach to the healing graft site. Therefore, caution should be used to avoid the development of arthrofibrosis. In the event that severe adhesions develop with loss of motion, the surgeon may perform an arthroscopic lysis of adhesions. Manual manipulations are not commonly performed for Carticel

patients due to the possibility of adhesion formation to the graft site.

Furthermore, as the chondrocytes grow and mature, graft hypertrophy may occur in a small number of patients, resulting in subjective reports of clicking and popping at approximately 3 months post-operatively. This may be addressed by modifying active and closed kinetic chain exercises to be performed with lighter resistance or in a symptom-free range of motion. Passive range of motion should continue to be performed to assist in the formation of a smooth articulation.

Emphasis of the rehabilitation program at this point is to facilitate a smooth, low-friction articular surface through the use of controlled passive range of motion and compressive loading (without sheer). Passive range of motion exercises should be performed manually by the rehabilitation specialist, as well as independently by the patient periodically throughout the day. It is recommended that the patient perform passive range of motion 4-6 times per day. Furthermore, the use of low resistance bicycle riding and aquatic therapy is recommended.

Reduction of Pain & Effusion

Numerous authors have studied the effect of pain and joint effusion on muscle inhibition. A progressive decrease in quadriceps activity has been noted as the knee exhibits increased pain and distention.[18, 19] Thus, the reduction in knee joint pain and swelling post-operatively is crucial to restore normal volitional quadriceps activity. Treatment options for pain and/or swelling may include analgesics, cryotherapy, high-voltage stimulation, ultrasound, and joint compression.

Restoring Muscle Function

The next principle involves restoring muscle function of the lower extremity. Inhibition of the quadriceps muscle is a common clinical enigma in the presence of pain and effusion during the acute phases of rehabilitation immediately following the implantation of Carticel. Electrical muscle stimulation and biofeedback are often incorporated with therapeutic exercises to facilitate the active contraction of the quadriceps musculature. This appears to facilitate the return of muscle activation and may be valuable additions to therapeutic exercises.[20]

Electrical stimulation may be used post-op day one while performing isometric and isotonic exercises such as quadriceps sets, straight leg raises, hip adduction and abduction, and knee extensions. Electrical stimulation may be used prior to biofeedback when the patient presents acutely with the inability to activate the quadriceps musculature. Once independent muscle activation is present, biofeedback may be utilized to facilitate further neuromuscular activation of the quadriceps. The patient must concentrate on neuromuscular control to independently activate the quadriceps during rehabilitation.

Exercises that strengthen the entire lower extremity, such as machine weights and closed kinetic chain exercises, should be included as the patient progresses to more advanced phases of rehabilitation. It is important that total leg strength be emphasized rather than concentrating solely on the quadriceps. Training of the hip, pelvis, core, and ankle located proximately and distally along the kinetic chain should be emphasized to assist in controlling force production and dissipation in the knee. In addition, the hip and ankle assist in controlling abduction and adduction movements at the knee joint.

PRINCIPLES of Rehabilitation Following **Carticel** Implantation

Proprioceptive and neuromuscular control drills of the lower extremities should also be included to restore dynamic stabilization of the knee joint postoperatively. Specific drills initially could include weight shifting side-to-side, weight shifting diagonally, mini-squats, and mini-squats on an unstable surface such as a tilt board (usually during Phase I of rehabilitation). Perturbations can further be added to challenge the neuromuscular system (usually during Phase II of rehabilitation). Additional exercises that may be performed include lateral lunges onto unstable surfaces and balance beam walking (usually during Phase III of rehabilitation).

Additionally, Carticel patients may benefit from use of orthotics, insoles, and bracing to alter the applied loads on the articular cartilage during functional activities. These devices can be used to avoid excessive forces by unloading the area of the knee where the implantation is located.

Unloader braces are often used for patients with subtle uncorrected abnormal alignments (genuvarum) and large or uncontained lesions, as well as in the presence of concomitant osteotomies and meniscal allografts.

Gradual Progression of Applied Loads

The next principle of rehabilitation following Carticel implantation involves gradually increasing the amount of stress applied to the injured knee as the patient returns to functional activities. The progression of weight-bearing and range of motion restoration, as previously discussed, involves a gradual advancement to assure that complications such as excessive motion restrictions or scar tissue formation are avoided while progressing steadily to avoid overstressing the healing graft site. An overaggressive approach early within the rehabilitation program may result in increased pain, inflammation, or effusion, as well as graft damage. This simple concept may be applied to the progression of strengthening exercises, proprioception training, neuromuscular control drills, and functional drills. For example, exercises such as weight shifts and lunges can be progressed from straight plane anterior-posterior or medial-lateral directions to involve multi-plane and rotational movements. Exercises using two legs, such as leg press and balance activities, can be progressed to single-leg exercises. Thus, the progression through the post-operative rehabilitation program involves a gradual progression of applied and functional stresses. This progression is used to provide a healthy stimulus for healing tissues while assuring that forces are gradually applied without causing damage.

Team Communication

An important principle of rehabilitation following Carticel (autologous cultured chondrocytes) implantation involves a team approach between the surgeon, physical therapist, and patient. Communication between the surgeon and therapist is essential to determine an accurate rate of progression based on the location of the lesion, size of the lesion, tissue quality of the patient, and the addition of concomitant surgical procedures. Also, communication between the medical team and patient is essential to provide patient education regarding the avoidance of deleterious forces, as well as compliance with precautions. Often, a preoperative physical therapy evaluation may be useful to mentally and physically prepare the patient for Carticel implantation and postoperative rehabilitation. Often times, the patient may become pain free earlier than expected, potentially endangering the Carticel implantation. As a general matter, the clinician should communicate to the patient that, although they may experience minimal symptoms, they should adhere strictly to the rehabilitation guidelines.

Please see accompanying full Prescribing Information inside back pocket.
Please see Important Safety Information for Carticel on page 2 and on back cover.

Notes:

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NOTE: This protocol has been established as a guideline only. Each patient must be assessed separately and the rehabilitation modified accordingly by the treating medical professionals.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Carticel® safely and effectively. See full prescribing information for Carticel.
Carticel (autologous cultured chondrocytes)
For Autologous Implantation
Initial U.S. Approval: 1997

----------INDICATIONS AND USAGE----------

Carticel is an autologous cellular product indicated for the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral or trochlea), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft). (1)

Carticel should be used only in conjunction with debridement, placement of a periosteal flap and rehabilitation. (1)

Carticel is not indicated for:

- treatment of cartilage damage associated with generalized osteoarthritis. (1)
- patients with total meniscectomy unless surgically reconstructed prior to or concurrent with Carticel implantation. (1)

----------DOSAGE AND ADMINISTRATION----------

For Autologous Implantation Only

- Carticel should be administered only by physicians who have completed Vericel's Surgeon Training Program. (2.3)
- Implantation of the Carticel product is performed during arthrotomy and requires both preparation of the defect bed and a periosteal flap to secure the implant.
- See the Carticel Surgical Manual, Vericel document #65021 for instructions on the performance of these procedures. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Each Carticel® vial of autologous cultured chondrocytes contains approximately 12 million cells per vial. (3)

----------CONTRAINDICATIONS----------

Do not use in patients with a known history of hypersensitivity to gentamicin, other aminoglycosides or materials of bovine origin. (4)

----------WARNINGS AND PRECAUTIONS----------

- The necessity of subsequent surgical procedures, primarily arthroscopic, following Carticel implantation is common. In the STAR study, 49% of patients underwent a subsequent surgical procedure, irrespective of relationship to Carticel. (5.1, 6.2)
- Carticel is not routinely tested for transmissible infectious diseases and may transmit diseases to the health care provider handling the product. Carticel is intended for autologous use only. (5.2)
- Pre-existing conditions, including meniscal tears, joint instability, or malalignment should be assessed and treated prior to or concurrent with Carticel implantation. (5.3)
- Carticel should not be used in patients who have previously had cancer in the bones, cartilage, fat or muscle of the treated limb. (5.4)

----------ADVERSE REACTIONS----------

The most common serious adverse events (> 5% of patients), derived from the STAR study include arthrofibrosis/joint adhesions, graft overgrowth, chondromalacia or chondrosis, cartilage injury, graft complication, meniscal lesion and graft delamination. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Vericel at 1-800-453-6948 or contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------USE IN SPECIFIC POPULATIONS----------

Use in children or patients over age 65 has not been assessed. (8)

See 17. for PATIENT COUNSELING INFORMATION

Revised: 11/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Carticel® is indicated for the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral or trochlea), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft).

Carticel should be used only in conjunction with debridement, placement of a periosteal flap and rehabilitation. The independent contributions of the autologous cultured chondrocytes and other components of the therapy to outcome are unknown.

Carticel is not indicated for the treatment of cartilage damage associated with generalized osteoarthritis.

Carticel is not recommended for patients with total meniscectomy unless surgically reconstructed prior to or concurrent with Carticel implantation.

2. DOSAGE AND ADMINISTRATION

For Autologous Implantation Only

2.1 Dosage

Patients in the Swedish series *[see Clinical Studies (14)]* received a wide range of cell doses per cm^2 of defect. Available data on 70 of 78 patients with femoral condyle defects showed a median dose of 1.6 million cells/cm^2 of defect. The middle 80% of these patients received from 0.64 million to 3.3 million cells/cm^2.

Each Carticel finished product vial contains approximately 12 million cells. Vericel provides a single vial for each defect measuring ≤ 7 cm^2. Two vials of Carticel are provided for defects 7 to 14 cm^2, and three vials are provided for defects > 14 cm^2. This is based on Vericel's greater than 10 years of experience with Carticel.

2.2 Handling Precautions and Preparation

2.2.1 Handling Precautions

The Carticel product is intended solely for autologous use. Prior to Carticel implantation, match the patient name and ID number on the certificate of analysis to the patient's chart and the patient ID on the shipping box, transport cylinder and vial.
Health care providers should employ universal precautions in handling the biopsy samples and the Carticel product [*see Risk of Transmissible Infectious Diseases (5.2)***].**
Refer to the Indications and Usage (1) and Warnings and Precautions (5) Sections for additional considerations regarding the use of Carticel.

2.2.2 Preparation

NOTE:
The exterior of the Carticel vial containing the cultured cells is NOT sterile. Follow strict sterile technique protocols.

When treating a defect that requires multiple vials of cells, resuspend, aspirate and inject one vial at a time.

1. Remove red plastic lid from vial. Wipe the vial surface and lid with alcohol.
2. Inspect vial contents for particulates, discoloration or turbidity. The cellular product appears as a yellowish clump in the bottom of the vial. Do not administer if contents appear turbid prior to cell suspension.
3. While holding vial in a vertical position, insert the needle of the intraspinal catheter into the vial. The needle must be positioned just above the fluid level. Slowly remove the inner needle from the catheter, leaving flexible tip behind. Attach a tuberculin syringe to catheter.
4. Lower the catheter tip into the media and position just above the cell pellet. Aspirate all the medium from the vial leaving only the cell pellet behind. Slowly expel medium back into the vial. This action will break the cell pellet and resuspend the cells in the medium.
5. Lower the catheter tip to the base of the vial and aspirate all contents into syringe, leaving the vial empty. Slowly inject the contents into the vial again. This will assure complete suspension of the cells. Repeat these steps as needed to ensure all cells are resuspended. Cell resuspension is complete when cell particles are no longer apparent, and the medium is a consistent, "cloudy" mixture. Aspirate all contents of vial into syringe. Always hold syringe vertical to keep an air pocket at the proximal end of syringe.

2.3 Administration

Implantation of the Carticel product should be restricted to physicians who have completed Vericel's Surgeon Training Program.

Implantation of the Carticel® product is performed during arthrotomy and requires both preparation of the defect bed and a periosteal flap to secure the implant. Complete hemostasis must be achieved prior to periosteal fixation and cell implantation. See the Carticel Surgical Manual, Vericel document #65021 for instructions on the performance of these procedures.

2.3.1 Implantation

1. Insert the catheter tip through the superior opening of the periosteal chamber at the site of the defect. Advance catheter to most inferior aspect of the defect.
2. Slowly inject a cell dose while moving the catheter tip from side to side and withdrawing the catheter proximally. This will ensure an even distribution of the cells throughout the defect.
3. Complete the implantation by closing the superior opening of the periosteum as instructed. See Carticel Surgical Manual, Vericel document #65021.

3. DOSAGE FORMS AND STRENGTHS

One vial of Carticel (autologous cultured chondrocytes) contains approximately 12 million cells.

4. CONTRAINDICATIONS

Carticel should not be used in patients with a known history of hypersensitivity to gentamicin, other aminoglycosides or materials of bovine origin.

Gentamicin is added to both the cartilage biopsy transport media and in the culture media used during the processing of Carticel. Residual quantities of gentamicin up to 5 µg/mL are present in the Carticel product.

Fetal bovine serum is a component in the culture medium used to propagate the autologous chondrocytes. Trace quantities of bovine-derived proteins may be present in the Carticel product.

5. WARNINGS AND PRECAUTIONS

5.1 Subsequent Surgical Procedures

Review of the data from the Study of the Treatment of Articular Repair (STAR) and the Registry Based Study (RBS) *[see Clinical Trials Experience (6.1)]* as well as the Carticel worldwide experience (adverse reactions solicited through the Cartilage Repair Registry (CRR) and spontaneous reports) as of November 21, 1997 showed that the occurrence of a subsequent surgical procedure, primarily arthroscopic, following Carticel implantation is common. In the STAR study, 49% of patients underwent a subsequent surgical procedure, irrespective of relationship to Carticel (6.2). Symptoms leading to arthroscopic intervention included catching, locking, clicking or pain. Patients who develop clinical signs of tissue hypertrophy, including catching or clicking, should be evaluated and arthroscopy may be indicated for treatment or further assessment.

5.2 Risk of Transmissible Infectious Diseases

The Carticel product is intended solely for autologous use. Patients undergoing the surgical procedures associated with Carticel are not routinely tested for transmissible infectious diseases. Therefore, the cartilage biopsy and the Carticel product may carry the risk of transmitting infectious diseases to the health care provider handling these tissues. Accordingly, health care providers should employ universal precautions in handling the biopsy samples and the Carticel product.

5.3 Pre-surgical Assessment of Comorbidities

The following conditions should be assessed and treated prior to or concurrent with implantation with Carticel:

1. Unstable meniscus tears should be repaired or resected.
2. If the patient has had a total meniscectomy, absent meniscus should be reconstructed.
3. Instability of the knee may adversely affect the success of the procedure and should be corrected. The anterior and posterior cruciate ligaments should be free of laxity as well as stable and intact. It is recommended that cruciate deficiencies be corrected.
4. Abnormal weight-distribution within the joint may adversely affect the success of the procedure and should be corrected. The tibial/femoral joint should be properly aligned. When treating trochlear defects, abnormal patellar mechanics should be assessed and corrected.

5.4 Product Safety and Sterility

The safety of the Carticel product is unknown in patients with malignancy in the area of cartilage biopsy or implant. The potential exists for *in vitro* expansion and subsequent implantation of malignant or dysplastic cells present in biopsy tissue. In addition, implantation of normal autologous chondrocytes could theoretically stimulate growth of malignant cells in the area of the implant, although there have been no reported incidents in humans or animals.

The Carticel product is shipped following a preliminary sterility test with a 48-hour incubation to determine absence of microbial growth. Final (14 day incubation) sterility test results are not available at the time of implantation.

6. ADVERSE REACTIONS

Information on the safety of implanted autologous chondrocytes is derived from the Study of the Treatment of Articular Repair (STAR) *[see Clinical Studies (14)]*, the Cartilage Repair Registry, the Swedish Series, and post-marketing adverse event reporting.

The most common serious adverse events (> 5% of patients) derived from the STAR study include arthrofibrosis/joint adhesion, graft overgrowth, chondromalacia or chondrosis, cartilage injury, graft complication, meniscal lesion and graft delamination. Only serious adverse events were collected in this study.

6.1 Clinical Trials Experience

The adverse reaction rates as well as the rate and type of subsequent surgical procedures from Carticel® studies of different designs cannot be directly compared amongst each other. Adverse reaction data from these studies do, however, provide a basis for identifying adverse reactions that may be related to product use and for estimating their frequency.

Study of the Treatment of Articular Repair (STAR)

In the STAR study [*see Study of the Treatment of Articular Repair (STAR) (14.2.2)*], patients who had experienced an inadequate response to a prior cartilage repair procedure underwent Carticel implantation to the index lesion. A total of 154 patients were implanted with Carticel; 28 patients discontinued the study early. The numbers of patients completing the 24 and 48 month follow-up visits are 136 and 115, respectively. Mean patient age was 35 years at consent. The majority of patients were Caucasian (135; 88%) and male (106; 69%).

Seventy-six (76) (49% of 154) patients underwent 113 subsequent surgical procedures (SSPs) on the treated knee, irrespective of relationship to Carticel, during the 4 year follow-up. Of the 76 patients, 52 patients had 1 SSP, 15 patients had 2 SSPs, and 9 patients had 3 or more SSPs. Sixty-one (61) (80%) of the 76 patients who had an SSP underwent a procedure within the first 24 months after implantation. The majority of patients, 83% (63 of the 76), underwent an arthroscopy or manipulation under anesthesia only. **Table 1** shows the interventions during SSPs in > 2% of patients.

Table 1: Interventions during Subsequent Surgical Procedures, Regardless of Relationship, in > 2% of Patients

Intervention	% of 154 Patients
Debridement of Cartilage Lesion[1]	31% (47/154)
Lysis of Adhesions	14% (21/154)
Synovectomy / Synovial Plica Excision	12% (19/154)
Other Debridement[2]	10% (16/154)
Chondroplasty	6% (10/154)
Meniscectomy	6% (10/154)
Loose Body Removal	5% (7/154)
Microfracture – Index Lesion	5% (7/154)
Scar Tissue Removal	5% (7/154)
Release of Patellar Retinaculum	4% (6/154)
Hardware Removal	4% (6/154)
Microfracture – New Lesion	4% (6/154)
Osteotomy	3% (5/154)

[1]Includes debridement of index lesion and other defects

[2]Includes debridement of other joint structures in addition to cartilage (e.g., patellar fat pad)

Lysis of adhesions was the most frequent surgical intervention performed in the first 6 months. After 6 months, cartilage debridement was the most frequently performed intervention. In the STAR study, 61% (46/76) of patients who required an SSP after Carticel did not meet failure criteria by either modified Cincinnati score or surgical criteria (e.g., graft delamination or surgical procedure violating the subchondral bone).

The most clinically significant interventions or findings involving the Carticel graft or periosteal patch are as follows: 3 Carticel grafts were completely removed and 1 was partially removed due to delamination. Partial delamination or fraying of the graft or periosteal patch was reported in 10 additional patients. Four (4) of these patients underwent reattachment/repair of the periosteal patch. Finally, a partially intact graft was found in 1 patient who was re-implanted. Detailed lists of interventions and findings that may have been associated with the graft or periosteal patch are presented in **Tables 1 and 2**, respectively.

Table 2 shows the serious adverse events (SAEs) that occurred in ≥ 5% of patients, regardless of relationship to study treatment.

Table 2: Most Frequent Serious Adverse Events (≥ 5% of Patients), Regardless of Relationship, in the STAR Study

Serious Adverse Events	% of 154 Patients
Arthrofibrosis/Joint Adhesions	16% (25/154)
Graft Overgrowth	15% (23/154)
Chondromalacia or Chondrosis	12% (18/154)
Cartilage Injury[1]	11% (17/154)
Graft Complication[2]	10% (15/154)
Meniscal Lesion	8% (12/154)
Graft Delamination	6% (9/154)
Osteoarthritis	5% (7/154)

[1]Encompasses cartilage injuries throughout the joint e.g., onset of new defects and tibial plateau fibrillation

[2]Includes periosteal patch complications, graft fraying or fibrillation

Registry Based Study (RBS)

Data from a cohort of 97 Carticel® treated patients, who were retrospectively evaluated in the Registry Based Study [*see Registry-Based Study (RBS) (14.2.1)*], showed that 39% (38/97) of patients had a SSP within 3 years of which 63% (24/38) were assessed as related to Carticel. Shaving or trimming (debridement) of overgrown tissue (hypertrophic) commonly relieved patients' symptoms. In the RBS, 67% (16/24) of patients who required arthroscopy after Carticel had a good clinical benefit in terms of improved function and relief of symptoms. **Table 3** shows the findings at surgery for the 38 patients who underwent a surgical procedure after Carticel.

Table 3: Most Frequent Findings (in ≥ 5% of Patients) at Subsequent Surgical Procedures in the Registry Based Study

Symptoms or Surgical Findings (MedDRA preferred term)	% of 97 Patients
Graft Overgrowth	10% (10/97)
Partial Graft Delamination	8% (8/97)
Chondromalacia	8% (8/97)
Arthrofibrosis/Joint Adhesions	8% (8/97)
Arthralgia	7% (7/97)
Synovitis	6% (6/97)
Meniscal Lesion	5% (5/97)
Loose Body	5% (5/97)

Swedish Series

Of 153 patients treated with autologous cultured chondrocyte implantation in the Swedish Series *[see Clinical Studies (14)]*, 22% (34/153) of patients experienced the adverse reactions presented in **Table 4** below.

Table 4: Initial ACI Experience Swedish Series Serious Adverse Reactions (Occurring at a frequency of 1% or more)

Serious Adverse Reactions	% of 153 Patients
Tissue Hypertrophy	See below
Intra-articular Adhesions	8%
Superficial Wound Infection	3%
Hypertrophic Synovitis	3%
Post-operative Hematoma	2%
Adhesions of the Bursa Suprapatellaris	2%
Hypertrophic Synovium	1%

About 1% of patients developed severe adhesions resulting in "frozen knee" and requiring lysis. Adverse reactions noted at a level of less than 1% included keloid-like scar, pannus formation, significant swelling of the joint, pain with post-operative fever, and hematoma following arthroscopy.

In this series, arthroscopy was scheduled to be undertaken at 18 months of follow-up, regardless of patient symptoms. Of the patients who had arthroscopy, 43% (37/86) had hypertrophic tissue.

Forty of the 85 patients had femoral condyle defects. Of these, 25% (10/40) of patients had some hypertrophic tissue noted at follow-up arthroscopy. Some patients had clinical symptoms that included painful crepitations or catching, and these symptoms generally resolved after arthroscopic resection of the hypertrophic tissue. Ten percent (10%) of patients with hypertrophy required additional treatment after hypertrophic tissue recurred following initial resection. Not all patients with tissue hypertrophy noted at arthroscopy were symptomatic.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Carticel®. Most of these reactions are reported voluntarily, and it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Furthermore, the reported frequency of spontaneous reports underestimates the true frequency of adverse reactions. As of July 31, 2006, approximately 12,500 patients have been implanted with Carticel and 559 patients have reported serious adverse reactions after treatment. The most frequently identified operative findings in these patients, in descending order of frequency, were graft overgrowth, graft delamination (partial or complete), arthrofibrosis, joint adhesions, meniscus lesion or tear, graft complications, chondromalacia, loose body in knee joint, and joint malalignment.

8. USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of Carticel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11. DESCRIPTION

Autologous cultured chondrocytes, the Carticel product, are derived from *in vitro* expansion of chondrocytes harvested from the patient's normal, femoral articular cartilage. Biopsies from a lesser-weight bearing area are the source of chondrocytes, which are isolated, expanded through cell culture, and implanted into articular cartilage defects beneath an autologous periosteal flap. Prior to final packaging, cell viability is assessed to be at least 80%.

Each single use container of autologous cultured chondrocytes has approximately 12 million cells aseptically processed and suspended in 0.4 mL of sterile, buffered Dulbecco's Modified Eagles Medium (DMEM). Both the biopsy transport media and the cell culture media contain gentamicin. Residual quantities of gentamicin up to 5 µg/mL may be present in the Carticel product.

12. CLINICAL PHARMACOLOGY

Hyaline cartilage forms the articular surface of the femoral condyle. Studies have shown that implantation of autologous chondrocytes into the articular defect can result in the development of hyaline-like cartilage *[see Clinical Studies (14)]*.[1,2,3,4,5] Normal hyaline cartilage consists of chondrocytes (≤ 5% total volume) and extracellular matrix (≥ 95% total volume). The matrix contains a variety of macromolecules, including type II collagen and proteoglycan. The structure of the matrix allows the hyaline cartilage to absorb shock and withstand shearing and compression forces. Normal hyaline cartilage also has an extremely low coefficient of friction at the articular surface. Damage to articular cartilage from acute or repetitive trauma often results in pain and disability. However, because hyaline cartilage is avascular, spontaneous healing of large defects is not believed to occur in humans.

A variety of surgical procedures have been used in attempts to promote repair of articular cartilage, and a few studies have evaluated the histology resulting from these interventions. Generally, procedures such as marrow stimulation techniques (MST) have been shown to produce fibrocartilage or hybrid mixtures of fibrocartilage and hyaline cartilage. Published data show that autologous chondrocyte implantation (ACI) is more likely than MST to result in hyaline-like cartilage at the repair site.[1,2,4,5] However, because of differences in study design, lesion size and concomitant patient conditions, these data are not sufficient to draw conclusions concerning the long-term correlation of histology and clinical outcomes.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity data are available for Carticel in animals or in humans. No studies on the effects of Carticel on fertility have been conducted.

13.2 Animal Pharmacology and/or Toxicology

Pre-Approval Studies

Bioactivity of autologous chondrocytes implanted under a periosteal patch was reported in the BLA for three rabbit studies[6,7,8] of up to 52 weeks duration post-implant and one dog study[9] of up to 18 months duration post-implant.

Rabbit Studies

- Histologic evaluations were performed at 8, 12 and 52 weeks. Improved healing of experimental defects implanted with autologous chondrocytes was observed compared to periosteal flap alone at 8, 12 and 52 weeks.

Dog Study

- Histologic evaluations were performed at 6 and 12 weeks and 12 and 18 months. Autologous chondrocytes showed improved healing compared to both empty defects and to defects covered with periosteum alone at 6 and 12 weeks. However, by the 12 and 18 month evaluations, the repair tissue had deteriorated so that no advantage of ACI over periosteum alone controls was demonstrated.

Beyond histologic variability of the defect site, no adverse tissue reaction was identified in any animals in these studies.

Post-Approval Studies

Five additional large animal, post-approval studies were performed.

Goat Studies

- Three of four goat studies were 16 weeks in duration. In the fourth study, the goats were sacrificed immediately after periosteal membrane placement. Despite difficulty in post-operative management of goats and resulting subchondral plate collapse in some animals in the 16-week studies, results from all four studies suggested that chondrocytes may contribute to histological repair of focal cartilage lesions. In the only bilateral joint study, serious subchondral collapse and uniformly poor repair resulted in inconclusive data. No safety issues were identified in any of these studies.

Horse Study

- The 8-week study included two experimental arms in order to model repair of cartilage lesions with or without subchondral penetration. Both models exhibited destruction/dislodgement of the periosteal flap; however, results suggested that chondrocytes may contribute to histologic repair in cartilage defects with subchondral penetration.

While the defects in all animal models exhibited highly variable repair tissue quality (resulting in only moderate histologic scores) the best repairs with implanted chondrocytes produced hyaline-like cartilage characterized by matrix predominating in type II collagen and saffranin-O or toluidine blue staining proteoglycan. Chondrocyte labeling in one of the rabbit studies[6] and in an independent study in goats by Dell'Accio et al[19] demonstrated that the hyaline-like matrix in these defects was the product of the implanted autologous chondrocytes.

14. CLINICAL STUDIES

14.1 Pre-Approval Studies

Clinical information regarding the use of autologous cultured chondrocytes was obtained from 2 open-label, observational studies consisting of a series of patients treated in Sweden and the Cartilage Repair Registry. Patients in the Swedish series received an autologous cultured chondrocyte product similar to Carticel®.

14.1.1 Swedish Series

The series consists of 153 patients who received autologous chondrocyte implantation for various defects of the knee. Patients presented with cartilage defects of the femoral condyle, patella, tibia, a combination of these, or osteochondritis dissecans, with or without comorbidity such as anterior cruciate ligament insufficiency requiring reconstruction.

Following autologous chondrocyte implantation, patients were followed for various durations. Clinical follow-up ranged from 1 week to 94 months; 86 patients had at least 18 months of follow-up. Most patients had arthroscopic evaluation; a subset had biopsy and histological evaluations. All patients were retrospectively classified as having one of three clinical outcomes: resumed all activities, some improvement, or no improvement. Clinical outcomes were also reported for patient subgroups including: 1) 40 patients with femoral condyle lesions, 2) 12 patients with osteochondritis dissecans lesions and 3) 22 patients who failed a prior debridement.

1) Clinical Outcome - Patients with Femoral Condyle Lesions

A total of 78 of 153 patients had femoral condyle lesions with or without co-morbidity. Patients had one or more defects ranging in size from < 1-20 cm^2. Of the patients with femoral condyle lesions, 40 were evaluable after at least 18 months (median = 25; range = 18 to 94 months). Clinical outcomes for the 40 patients are summarized in **Table 5.**

Table 5: Patient Response to Treatment

Defect	Resumed All Activities	Some Improvement	No Improvement	Total Patients
Femoral Condyle	7 (29%)	8 (33%)	9 (38%)	24
Femoral Condyle plus other Non-Cartilage Repair	4 (25%)	9 (56%)	3 (19%)	16
Total	11 (28%)	17 (42%)	12 (30%)	40

2) Clinical Outcome - Patients With Osteochondritis Dissecans Lesions

Of the 12 patients who received autologous cultured chondrocytes for treatment of an osteochondritis lesion, 6 of the 12 had "resumed all activities", 4 had "some improvement" and 2 had "no improvement" after the 18-month (median = 25; range = 18-94 months) follow-up period.

3) Clinical Outcome - Failed Earlier Procedures

Debridement of the cartilage defect is often performed along with administration of autologous cultured chondrocytes. To help differentiate the effects of the autologous cultured chondrocyte implantation procedure from those of debridement alone, an analysis was performed on 22 patients who had failed prior debridement and had a follow-up period after autologous cultured chondrocyte implantation which was at least as long as the time period to failure of their initial debridement. At the end of follow-up, 5 of the 22 patients had a functional outcome rating of "resumed all activities", 8 of the 22 patients had a rating of "some improvement" and 9 of the 22 patients had a rating of "no improvement". Thus, 13 of the 22 patients (59%) who had failed an earlier debridement had outcomes that were more favorable and durable following autologous cultured chondrocyte implantation than their previous debridement without cells.

Histological Outcome

Twenty-two (22) patients in the Swedish series had histological evaluation of biopsies from the implant site one or more years after their autologous chondrocyte implantation. Fifteen (15) of those patients had defects of the femoral condyle and 7 had defects of the patella. Six (6) of the 15 femoral condyle biopsies showed hyaline-like cartilage, 5 had a mixture of hyaline and fibrocartilage, and 4 had only fibrocartilage. Of the 6 biopsies with hyaline-like cartilage, 2 had minimal to no surface irregularities and 4 had some surface irregularities (e.g., fissures, fibrillations, etc.).

Arthroscopic Outcome

As an objective outcome evaluation, 86 of the 153 patients had a follow-up arthroscopy for investigational purposes at 18 months or more post-implantation. In some cases, the quality of repair observed at arthroscopy was considered to be supportive of the clinical or functional outcomes. A substantial number of patients were noted at arthroscopy to have tissue hypertrophy *[see Adverse Reactions (6)].*

14.1.2 Cartilage Repair Registry

The Cartilage Repair Registry (CRR) was established upon the introduction of Carticel® into orthopedic practice in March of 1995. The CRR was designed to prospectively collect the clinical outcomes of Carticel and other cartilage repair treatments for chondral lesions in the knee. Clinical data were collected at baseline arthroscopy, implantation, intervals of 6 and 12 months, and annually thereafter; adverse reaction data were collected on an ongoing basis through CRR adverse reaction collection and spontaneous reporting. Inclusion in the CRR was based on a qualifying event that was defined as a knee arthroscopy in which a chondral lesion was identified and a cartilage biopsy was harvested. Participation in the CRR was voluntary, and not all patients biopsied or implanted were included. As of November 21, 1997, 891 patients had been implanted worldwide, and 644 of these patients were included in the CRR. Functional outcomes were based on responses to a modified version of the Cincinnati Knee Rating System.

Data from a subset of 191 US patients in the CRR as of December 31, 1996 who had undergone repair of lesions on the femoral condyle (medial, lateral or trochlea) were assessed to support licensure. Patients were between the ages of 15-57, 66% (126/191) were male, and 34% (64/191) were female and one patient's gender was not reported. Of these 191 patients, 38 had at least 12 months of follow-up. At study baseline, these 38 patients' mean rating of overall condition was 3.2, which is defined as fair to poor: limitations that affect activities of daily living-no sports possible. At 12 month follow-up, these patients reported an overall condition score of 6.4 defined as good: some limitation with sports but can participate if patient compensates. Although these patients were rated according to outcome measurements different from those used in the Swedish series, the results were consistent with the Swedish experience.

14.2 Post-Approval Studies

Two post-approval studies were conducted and completed as a condition of approval for Carticel®: the Registry Based Study (RBS) and the Study of the Treatment of Articular Repair (STAR).

14.2.1 Registry-Based Study (RBS)

The RBS was a retrospective analysis of data collected for a cohort of 97 US patients treated between March of 1995 and March of 1997. Of the 97 patients enrolled, 95% completed 1-year follow-up, 80% completed 2-year follow-up and 74% completed 3-year follow-up. Of these 97 patients, 44 were part of the subset of 191 US patients in the CRR described above. A limitation of this study is the lack of a control group. Patients included in this study had a prior non-Carticel cartilage repair procedure (e.g., debridement or marrow stimulation procedure) performed at the time of the index arthroscopy, subsequently failed this procedure and went on to receive Carticel. In the 5 years prior to the index arthroscopy for the study, this patient population had received prior knee surgeries to include: 47% (46/97) of patients had at least one debridement/lavage of a cartilage defect, 25% (24/97) of patients had a bone marrow stimulation procedure, 31% (30/97) had at least one diagnostic arthroscopy, 30% (29/97) had at least one meniscus repair/menisectomy and 10% (10/97) of patients had a ligament repair/reconstruction performed on the treated knee.

Using a modified Cincinnati Knee Rating System at study baseline, this patient population had a mean overall condition score of 3.1 defined as fair to poor: limitations that affect activities of daily living-no sports possible. Patients included were between the ages of 16-56, 69% (67/97) were male and 31% (30/97) were female. For the type of defect, 62% (60/97) of the defects were acute while 37% (36/97) were chronic. Of the treated defects, 75% (73/97) were treated on the medial femoral condyle (MFC), 26% (25/97) on the lateral femoral condyle (LFC) and 19% (18/97) on the trochlea. Adverse reactions collected during this study are provided in Adverse Reactions (6).

14.2.2 Study of the Treatment of Articular Repair (STAR)

The STAR study was an open-label within patient comparison of a prior non-Carticel (index) procedure to implantation of Carticel for articular cartilage defects of the distal femur. All patients had experienced an inadequate response to a prior non-Carticel surgical treatment, defined as both: a) patient and surgeon agreement that the patient's symptoms/function required surgical re-treatment of the defect and b) the patient's rating of the overall condition of the knee was a score ≤ 5 using the Modified Cincinnati Knee Rating System. In this patient population, the median time to meet the failure criteria was 3.4 months for the prior non-Carticel procedure and 90% of patients failed within 10.3 months. Patients who met these criteria were treated with Carticel and assessed every 6 months for up to 4 years.

Treatment failure for Carticel was defined as any of the following: a) the patient underwent surgical retreatment that violated the subchondral bone or reimplantation with Carticel for the same index defect, b) complete delamination or removal of the graft, or c) the patient's rating of the overall condition of the knee using the Modified Cincinnati Knee Rating System failed to improve from the baseline knee score over 3 consecutive 6-month intervals.

A total of 154 patients were treated with Carticel. At the index surgery required for study entry, patients had one or more of the following interventions: 120 patients (78%) had debridement, 44 patients (29%) had microfracture, 18 (12%) had subchondral drilling, 10 (6%) had abrasion arthroplasty, and 7 (5%) had an osteochondral autograft. The mean lesion size was 4.6 (± 3.2, SD) cm^2. Fifty patients (32%) had multiple lesions in the reference knee and 29 patients had Carticel implanted in more than one lesion. Lesions that were implanted were located on the medial femoral condyle in 109 patients, lateral femoral condyle in 32 patients and trochlea in 46 patients. Forty patients (26%) had lesions which involved osteochondritis dissecans (OCD).

Of the 154 patients treated with Carticel, 28 patients discontinued the study early. The numbers of patients completing the 24 and 48 month follow-up visits are 136 and 115, respectively. The majority of Carticel patients (N= 117) did not meet failure criteria during the study. By the end of the study, a total of 37 patients met the treatment failure criteria. Results for the 40 patients with OCD lesions were comparable to the total study population as 34 (85%) did not meet the failure criteria for the study and 6 (15%) failed treatment with Carticel. **Table 6** illustrates, during each year of follow-up, the number of patients who failed Carticel by the surgical criteria along with the number of patients who failed by the Overall Modified Cincinnati scale criteria.

Table 6: Category and Timing of Treatment Failure for Patients who Met Treatment Failure Criteria (N=37)

	1 Year	2 Years	3 Years	4 Years	Total
Patients who Failed During the Interval	14	11	11	1	37
Surgery criteria	0	5	5	1	11
Overall Modified Cincinnati Scale criteria	14	6	6	0	26

The Overall Modified Cincinnati mean baseline score for the patient population as a whole was 3.26, poor: significant limitations that affect activities of daily living, to fair: moderate limitations that affect activities of daily living, no sports possible. At 48 months, the mean score was 6.39, good: some limitations with sports but can participate/compensate. The improvement was statistically significant. **Table 7** shows the improvement in the Overall Modified Cincinnati score over time.

Table 7: Mean Overall Modified Cincinnati Score at Baseline and Follow-up Visits

Visit	Baseline N=154	Month 12 N=146	Month 24 N=131	Month 36 N=104	Month 48 N=101
Overall Modified Cincinnati Score[1] Mean (SD)	3.26 (1.02)	5.58 (1.99)	5.92 (2.08)	5.87 (2.19)	6.39 (2.31)

[1]Scores are for patients who returned for follow-up. Patients who failed by score criteria are included and patients who failed by surgical criteria are excluded from the scores for therapeutic success after the failure criteria were met.

In addition to the change over time in activity level as measured with the Overall Modified Cincinnati Scale, there were similar and consistent changes in knee symptoms and function as measured with the Knee Injury and Osteoarthritis Outcome Score (KOOS), a measure of knee-specific symptoms and function consisting of the following five subscales: pain, symptoms, sports and recreation, knee-related quality of life, and activities of daily living. At 12 months post-Carticel® implant, the mean improvement from baseline for the patient population as a whole in each subscale was as follows: pain 19 (N = 146), symptoms 15 (N = 147), sports and recreation 17 (N = 129), knee-related quality of life 18 (N = 147), and activities of daily living 18 (N = 145). At 48 months post-Carticel implant, the mean improvement from baseline was as follows: pain 24 (N = 100), symptoms 19 (N = 101), sports and recreation 31 (N = 86), knee-related quality of life 32 (N = 101), and activities of daily living 23 (N = 99).

Adverse reactions collected during this study are provided in Adverse Reactions (6).

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16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

The Carticel product, NDC 69866-1025-1, consists of viable, autologous cells packaged and labeled for implantation within specified time limits. Each vial contains approximately 12 million autologous cells for a single implantation procedure.

The shipping vials containing chondrocytes are accompanied by a technical data sheet with detailed specifications for the processed cells. The vial(s) of cells is placed within secondary packaging capable of maintaining the appropriate storage temperature and cell viability for up to 72 hours.

16.2 Storage and Handling

The Carticel® transport box should be held at room temperature and remain closed until the time of implantation to ensure proper storage conditions for the cells.

Do Not Refrigerate, Freeze, or Incubate the Carticel Shipping Container or its Contents.

Do Not Sterilize.

If the Vial is Damaged or Sterility has been Compromised, Do Not Use.

17. PATIENT COUNSELING INFORMATION

Patients receiving autologous cultured chondrocytes for treatment of an articular cartilage defect should receive the following information and instructions.

- Physical activity should be resumed according to the rehabilitation plan recommended by the physician. Generally, protected weight bearing is recommended for the first 6 to 8 weeks following implantation. The patient should receive specific instructions on crutch use, ambulation and weight bearing advancement on the treated limb.
- If pain starts to develop as the next level of activity is increased, decrease activity to the former level until the pain resolves.
- If exercise causes pain and/or swelling, reduce the amount of physical activity.
- Swelling should be controlled using ice packs.
- Patient adherence to the prescribed rehabilitation program is important and activity at variance from the rehabilitation program may compromise clinical benefit from Carticel.
- At anytime during the rehabilitation process or after, if sharp pain with locking or swelling is experienced, contact the physician for medical advice.

Vericel Corporation
64 Sidney Street
Cambridge, MA 02139-4136 USA
Telephone: 800-453-6948 or 617-588-5566
Fax: 844-333-2847

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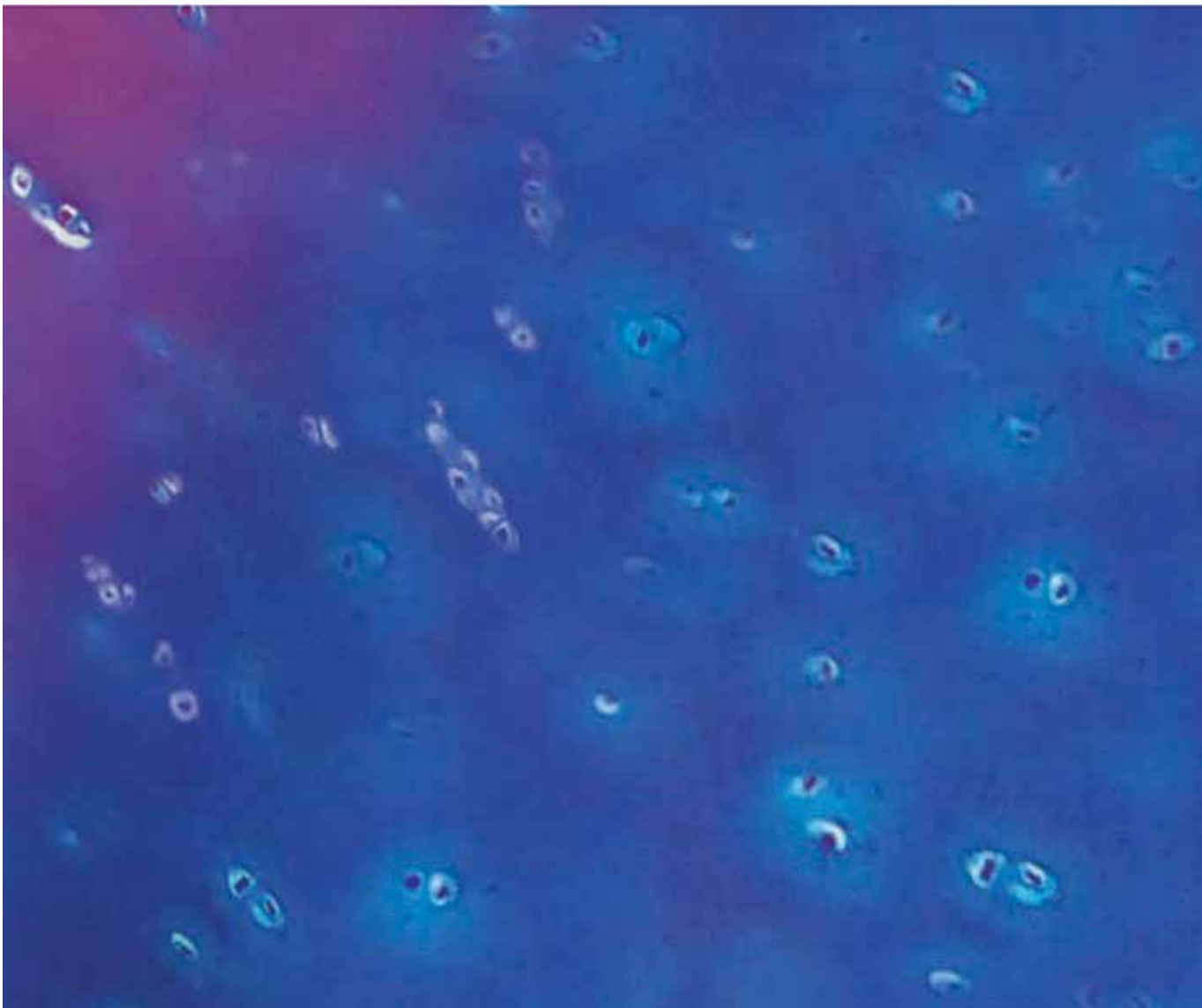

Important Safety Information

Carticel® (autologous cultured chondrocytes) is an autologous cellular product indicated for the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral or trochlea), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft).

Carticel should only be used in conjunction with debridement, placement of a periosteal flap and rehabilitation. The independent contributions of the autologous cultured chondrocytes and other components of the therapy to outcome are unknown.

Carticel is not indicated for the treatment of cartilage damage associated with generalized osteoarthritis.

Carticel is not recommended for patients with total meniscectomy unless surgically reconstructed prior to or concurrent with Carticel implantation.

Please see accompanying full Prescribing Information inside pocket.

VERICEL

Vericel Corporation
64 Sidney Street
Cambridge, MA 02139
800-453-6948
www.Carticel.com