SUMMARY FOR BASIS OF APPROVAL

BLA Ref. No. 96-0372 Drug Licensed Name: Autologous Cultured Chondrocytes
Drug Trade Name: Carticel™

Manufacturer: Genzyme Tissue Repair
64 Sydney Street
Cambridge, Massachusetts 02139-4136

HISTORY OF REGULATORY STATUS

A variety of mechanisms have been used in the past to regulate somatic cell products. Depending on the make-up and the intended use of the product, some were regulated as biologics, others as devices, others not at all. With the rapid growth of interest in and development of such therapies in recent years, the regulatory approaches have been under careful consideration and evolution. Genzyme Tissue Repair (GTR) began marketing Carticel™ in 1995 based upon indications from the agency that, being an autologous cell therapy, Carticel™ would not be regulated. Later that year, CBER notified GTR that CBER considered Carticel™ to be a somatic cell therapy product as defined in the October 14, 1993 Federal Register notice concerning human somatic cell and gene therapy products and advised GTR that marketing approval would be required. GTR submitted a request for product designation to clarify agency jurisdiction; the agency notified GTR it could continue to market Carticel™ while jurisdiction was under consideration and policy under development. After substantial public consultation, on May 28, 1996, the agency issued a document entitled "Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated Ex Vivo and Intended for Structural Repair or Reconstitution" (these cells are referred to as MAS cells), which notified GTR and other sponsors of MAS cell products that they were involved in the manufacture of biological products and that, effective November, 1997, those products could be used only under approved licensed application or IND exemption.

I. INDICATION FOR USE

Carticel™ is indicated for the repair of clinically significant, symptomatic, cartilaginous defects of the femoral condyle (medial, lateral or trochlear) caused by acute or repetitive trauma.

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

Carticel™ should 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. Data regarding functional outcomes beyond 3 years of autologous cultured chondrocyte treatment are limited.

II. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

Carticel™ is supplied as viable autologous culture chondrocytes in buffered medium packaged in single-use vials intended for implantation after resuspension. Each single use vial has approximately 12 million cells aseptically processed and suspended in 0.4 ml of sterile, buffered Dulbecco's Modified Eagles Medium (DMEM). Cell viability is assessed to be at least 80%. The product contains no preservative. Carticel™ is supplied in packs of 1-4 single-use vials depending upon the size of the defect.

Implantation of Carticel™ product is performed during arthrotomy and requires both preparation of the defect bed and placement of a periosteal flap to secure the implant. Complete hemostasis must be achieved prior to periosteal fixation and cell implantation.

In a series of experiments conducted in Sweden, patients 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.

III. MANUFACTURING AND CONTROLS

A. Manufacturing and Controls

The Carticel™ product consists of autologous cultured chondrocytes produced from a biopsy of healthy cartilage obtained from the patient's knee. Carticel™ is a MAS cell product as defined in the Federal Register Notice of May 28, 1996, " Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated Ex Vivo and Intended for Structural Repair or Reconstitution." The procedure for Carticel™ is similar to that published by Brittberg et. al. in Götenburg, Sweden (New Eng. J. Med. 331:889, 1994). Biopsy specimens of cartilage obtained during arthroscopy are shipped to GTR using transport kits supplied by the company. The biopsies are enzymatically digested and freed cells are expanded in cell culture flasks at 37°C. Cells obtained from biopsies from different patients are physically separated within the incubator. After limited expansion, cells are cryopreserved until a request is received for implantation. Thawed cells are further expanded, and the time period for expansion is determined by the interval required for producing the required numbers of cells to be used for implantation. This number of cells may vary from 12 million (one vial) to 48 million (four vials), depending upon the number of cells required to fill the patient's articular cartilage defect. Cells are processed for assembly in a dedicated room and laminar flow biological safety cabinet used only for product assembly. The cells in the tissue culture flasks are treated with trypsin to remove them from the plastic substrate followed by washing. Final product is sampled for the testing, filled into glass vials fitted with rubber stoppers by crimping, and shipped to the surgeon for implantation.

Neither the patient nor the patient's expanded cell culture is tested for infectious viral agents. Therefore, all products are considered to be subject to biohazard precautions and labeling. All biopsy samples and cell cultures are handled separately within biological safety cabinets which are decontaminated between each use.

Raw materials and packaging components to be used in the production of Carticel™ are subjected to appropriate quality control evaluations before they are accepted for use in manufacture.

GTR has instituted a number of process controls during the production process to ensure integrity of the final product. Cell cultures are sampled at various points during the manufacturing process and tested for bacterial and fungal contamination. In addition, the cells are closely monitored throughout the cell expansion process for morphological characteristics. The manufacturing process is periodically monitored for the potential of mycoplasma contamination. Final product is screened for, and must pass the lot release specifications shown in Table 1. Each patient's cellular product is an independent lot. The requirement for lot identity and purity is met by cellular morphological assessment and potency is assessed by cell count and viability. Product not passing the lot release specifications may be, depending on the release criterion, retested according to applicable SOP. Failure of tests results in lot rejection.

Table 1. Carticel™ Lot Release

Release Specifications	Methods	Range
Microbiologic Sterility	Direct inoculation (72 hr prior to assembly	No growth by direct inoculation
Endotoxin	LAL	≤ 3EU/ml
Viability	Trypan blue	≥ 80% dye-excluding cells
Morphology	Microscopic Exam	≥ 80% typical chondrocyte morphology
General Safety Test Alternative	Trypan Blue	≥ 80% dye excluding cells
	Microscopic Exam	≥ 80% typical chondrocyte morphology
(Alternative is 3 parts; all criteria must be met)	Elution assay for cytotoxicity on indicator cells (48-72 hr prior to assembly	Score of 0: No cell death above background

Because the live cells must be implanted within 72 hours of final harvest, the product has been exempted from the requirements of sterility testing as specified in 21 CFR 610.12. To provide assurance of product sterility, GTR removes a sample of culture supernatant 72 hours prior to harvest. Product is released for shipment

based upon a negative reading of this test. A second sterility test is then performed on a product sample taken at the conclusion of harvest, cell washing and resuspension. Both samples are tested for 14 days in conformance to procedures outlined in 21 CFR 610.12. Any positive sterility result from the sample obtained from the final product is immediately reported to the physician. In addition, because of the time constraints associated with shipment of viable cells, an alternative method for the General Safety test described in 21 CFR 610.11 was developed which consists of a combination of three assays described below under "Equivalent Methods."

B. Equivalent Methods

The agency has accepted two equivalent methods under 21 CFR 610.9 for Carticel™, including one for rabbit pyrogen testing (21 CFR 610.13) and a combination set of tests for General Safety Testing (21 CFR 610.11).

The alternative test for rabbit pyrogens includes use of one of two Limulus Amebocyte lysate tests for bacterial endotoxin (Kinetic Chromogenic Assay or the Gel Clot Assay). Tests have been developed and validated according to the 1987 FDA Guideline on Endotoxin Tests. Both tests have been qualified to the rabbit pyrogen assay by parallel testing.

The alternative test for the General Safety Test includes a group of three assays. The assays comprise characterization of chondrocyte morphology, cell viability, and an assay adapted from the MEM Elution Assay (USP) for cytotoxicity using the murine cell line, L929, as the indicator. The assays have been validated using toxic substances found in the manufacturing facility, and material from patient lots of Carticel™. Release criteria have been set based on validation data. The agency has determined that the combination of these three tests provides assurance of safety equal to that of the General Safety Test (21 CFR 610.11).

C. Stability Studies

A dating period of 72 hours has been given to the Carticel™ product based on test results from three product lots. The three lots were shipped to a clinical site and then returned to GTR for testing. The primary stability indicating assay was cell viability. Additional studies to validate the dating period under a variety of shipping conditions are ongoing.

D. Validation

Utility systems, manufacturing equipment, manufacturing processes and analytical methodologies used in the production of Autologous Cultured Chondrocytes have been validated according to established written procedures. Procedures are in place to ensure the regular maintenance of equipment and the regular monitoring of environmental conditions within the production facilities.

E. Labeling

The container, package and package insert labeling are in compliance with the applicable regulations (21 CFR 201.1 - 201.57, 610.60, 610.61 and 610.62). The Cartilage Biopsy transport kit labeling is in compliance with 21 CFR 801.1 - 801.15 and 801.109. The product trademark, Carticel™ , is not known to conflict with any other drug product trademark.

F. Establishment Inspection

A prelicense inspection of Genzyme Tissue Repair's Cambridge and Framingham, Massachusetts production facilities was conducted by personnel from the Center for Biologics Evaluation and Research and the New England District Office, December 2-6, 1996. The firm is deemed in compliance after review of all corrective actions taken to address the observations noted on the Form FDA 483 that was issued.

G. Environmental Impact Analysis Report (EIAR)

An environmental assessment was filed, reviewed and found to be acceptable. A finding of no significant impact (FONSI) is attached.

IV. PHARMACOLOGY

A. Pharmacologic and Toxicologic Studies

The activity and safety of Autologous Cultured Chondrocyte (AuCC) implantation under a periosteal flap (PO) was evaluated in one study conducted by GTR in dogs, and two selected articles which reported findings in rabbits. Labeling of AuCCs was conducted either by a retroviral vector encoding beta-galactosidase, or by tritiated thymidine, to evaluate the persistence of the implanted chondrocytes, and to evaluate their contribution to the chondrocyte population, later isolated from biopsies of the defect fills. In general, animals were subjected to surgically induced, bilateral defects in weight-bearing joints. Defects on one side served as an untreated control (either untreated or PO); the treated side provided data on results of PO/AuCC.

1. A study was conducted in dogs (hound-type mongrels, 30 kg average) to evaluate the activity and safety of Carticel™ under controlled conditions, using a weight-bearing model of femoral condyle defects. Experimental groups were defined by the length of time on study (5 dogs/group); groups were sacrificed at 4 time points - 6, 13, 26, and 52 weeks. To evaluate the longevity of the implanted AuCCs, cells from 1 dog/group were labeled with a retroviral vector designed to encode beta-galactosidase and permit detection of the implanted AuCCs. No data on long-term graft durability or joint function were gathered. Defects were intended to be created down to, but not including the calcified cartilage layer. This was difficult to accomplish uniformly because canine cartilage is thin compared to that in the analogous human joint. Thus, some defects resulted in injury of the subchondral bone plate; in several defects, complications from disturbing this deep layer arose[1]. AuCCs were administered using 2 million cells/defect. Interpretation of data is limited because data tables and analysis are at this date still incomplete; the bulk of the analysis was framed based on the most complete reporting of the 6 month group results. At 13 weeks, a greater degree of defect fill was seen in PO/AuCC-treated, compared to control lesions. Two of 5 animals with beta-galactosidase-transfected AuCCs showed slight staining, indicating some of the original cells were present in the defect, similar to the results in the rabbit study by Grande et. al. (see below). The relative contribution of the original AuCCs implanted versus chondrocytes from other sources could not be quantitatively determined. At 26 weeks, in both treated and control defects, cartilage samples were positive for hyaline-type cartilage, with greater fill levels in PO/AuCC treated defects. At 52 weeks, all defects exhibited similar degrees of healing quality and fill level, showing the majority of the benefit from PO/AuCC treatment was seen early in healing. Examples of hyaline and fibrocartilage were evident in both control (PO treated or untreated) and treated (PO/AuCC) sites. This animal model was not expected to exhibit spontaneous healing in the untreated defects, based on other examples in the canine literature. No dogs within this 1 year study period exhibited exuberant cartilage development.

2. (D. Grande, M. Pitman, L. Peterson, D. Menche, and M. Klein. J. Orthop. Res. 7:208,1989). This article reported short-term activity of PO versus PO/AuCC treatment in the rabbit model of experimental cartilage injury out to only one early time point, 6 weeks following surgery. Cells were labeled to evaluate the residence time of AuCCs and the total contribution of the AuCCs to the chondrocyte population found in the cartilage at 6 weeks post-healing. To accomplish this, AuCCs were isolated in a manner similar to the clinical methods, and in some animals, cells were additionally labeled with tritiated thymidine. Cells (1 million/defect) were then implanted under a

[1] A number of published studies have indicated that puncturing the subchondral plate can introduce an influx of mesenchymal stem cells with chondrogenic potential, as well as blood. These factors may affect the nature, extent, or quality of the defect healing process and variability in subchondral penetration can therefore confound the results of the study.

periosteal flap; 95% of the AuCCs were labeled. Rabbits were sacrificed at 6 weeks after the implantation and tissues in the defects were examined. Autoradiographic examination of the filled defects over time revealed that some cells from the original implant remained, but only 8% of the cells were labeled. The source of the other cells present in the healing cartilage was not known. This did provide evidence that some cells do remain viable in the graft and may contribute to healing the defects. However, the study was not designed to indicate the source of the other 92% of cells in the defect or to determine the durability or viability of the implanted chondrocytes over an extended period of time. Evaluation of the joints revealed a lower incidence of moderate to severe synovitis in the PO/AuCC joints, compared with PO joints (7/10 vs. 2/10). The mean graft healed area at the 6 weeks point (study termination) was 82% (PO/AuCC) versus 19% (PO).

3. (M. Brittberg, A. Nilsson, A. Lindahl, C. Ohlsson, and L. Peterson. Clin. Orthopeaedics Rel. Res., 326: 270,1996). This study evaluated a rabbit model of chronic non-weight bearing (patellar) cartilage defects and autologous cell (AuCC) repair. New Zealand White rabbits (young adults, age $\geq$ 4 months, 7-12 rabbits per group) were evaluated, with groups designated for sacrifice and histologic examination at either 8, 12, or 52 weeks. Stained tissue was assessed for degree of healing (evaluating 4 sections/patellar defect) and joints were assessed for synovitis; comparison was made per rabbit between treated and control knees but was not conducted in a blinded fashion. The quality of tissue repair was further assessed by a complex collective point scoring system published by O'Driscoll (S. O'Driscoll, Y. Miura, and S. Gallay. Trans. Orthop. Res. Soc. 15:210, 1990); normal cartilage scored a total of 24 points. Repair tissue was of better quality and quantity (more complete fill) in treated knees at 52 weeks compared to that seen in controls. The appearance of the repair tissue on a macroscopic level was white and smooth, but containing some depressed areas either centrally or at the margin of the defect. Joints lacked evidence of synovitis and appeared to possess a full range of passive motion. However, small fissures were evident in the central areas of many sites, which introduces some questions regarding long-term repair durability. Tissue scores at week 52 indicated that PO/AuCC-treated sites reached a mean score of 19/24; PO-control sites scored only 7/24. PO/AuCC-treated sites showed maximum fill at 52 weeks (87%). PO-control sites reached their maximum fill at 8 post-operative weeks (approximately 30% filled). Despite some limitations in data analysis, evidence presented indicated that more complete healing occurred in the treated sites, which appeared to have durability up to a year; no exuberant cartilage was evident, and rabbits which survived surgery tolerated the procedure well. This procedure was conducted using procedures similar to those used clinically, with the exception that this model was conducted using patellar lesions.

B. Conclusions from Animal Studies

The preclinical studies provided adequate evidence of local and systemic safety of Carticel™ over a period of a year. Studies in rabbits (but not dogs) showed improved healing in AuCC/PO treated joints when compared to PO-treated controls. Studies in both rabbits and dogs provided data which supported clinical safety out to 1 year following surgery for the AuCC/PO implantation procedure. The appropriateness of various animal species as biologic models of human cartilage repair has not been specifically evaluated, therefore there is no *a priori* reason to regard results from one species as more predictive of clinical results than another. The animal studies did not capture data on the biomechanical properties of healed cartilage or joint functional assessments, nor did they provide quantitative data on healed cartilage tissue architecture and tissue composition; study interpretation was thus limited to assessment of local tolerability and activity. Further studies in the literature indicated that chondrocytes found in healed defects might derive from multiple sources, including the mesenchymal cells, the implanted AuCCs, and the PO implant; additionally, each of these cell types may serve as sources for paracrine growth factors in the microenvironment of the defect.

V. MEDICAL

A. Background

Articular (hyaline) cartilage of the femoral condyle consists of chondrocytes (approximately 5% or less) and extracellular matrix (95% or more) produced by the chondrocytes. The extracellular matrix contains a wide variety of macromolecules, such as Type II collagen and proteoglycan, which impart the unique biomechanical properties of hyaline cartilage. With an intact articular surface, hyaline cartilage has an extremely low coefficient of friction. The proper ultrastructural arrangement of the matrix allows articular cartilage to provide significant shock absorbing capacity and to withstand shearing and compression forces.

Because hyaline cartilage is avascular, spontaneous healing of clinically symptomatic defects of articular cartilage has not been well documented in humans. Complete healing consists of restoring the chondrocytes and normal extracellular matrix as well as the articular surface. A variety of surgical techniques have been attempted to promote healing of hyaline cartilage. In general, these techniques appear to produce fibrocartilage rather than hyaline cartilage. Fibrocartilage contains Type I collagen (which is not present in hyaline cartilage) and is less durable than hyaline cartilage.

Therapy with Carticel™ involves generation of cells from autologous chondrocytes and administration into clinically significant articular cartilage defects. First, hyaline cartilage in a lesser weight bearing area of the femoral condyle of the

affected knee is harvested. The chondrocytes from this biopsy are then expanded approximately 10 to 20 fold (although occasionally more) *in vitro* by cell culture techniques over a period of weeks to generate the Carticel™ product. These cells are then implanted under a periosteal flap into the hyaline cartilage defect.

B. Clinical Studies

GTR submitted clinical information regarding Carticel™ from two principal sources: a Swedish series and a US registry database. GTR requested approval for Carticel™ as a treatment for patients with articular cartilage defects of the femoral condyle. Patients in the Swedish series received an autologous cultured chondrocyte (AuCC) product for implantation which was prepared in a manner very similar to that used to produce Carticel™ the U.S. product.

1. Swedish Series

Prior to the announcement of any formal FDA regulations for this product class, the sponsor retrospectively collected data on 153 consecutive patients treated by orthopedic surgeons in Sweden. Available information from the published literature were reviewed to provide a historical control.

Sponsor Data Collection and Efficacy Analysis

GTR reported on data derived from 3 sources: 1) retrospectively generated case report forms (CRF), 2) a questionnaire sent to patients who had completed at least 1 year of follow-up following surgery, and 3) biopsy data (available for 22 of the 23 initial patients and from 3 patients treated later in the series). Principle evaluations were based on 82 patients with response to the questionnaire. The responses reflected the patients' clinical assessment at a single point in time. Baseline data regarding patient function, pain, and activity were unavailable for analysis, as were data regarding patient progress following therapy with AuCC implantation, appearance of the lesion at arthroscopy, histologic appearance of repair tissue (except for 25 patients), and rehabilitative schemes.

Patients by Procedure Groups as Defined by Sponsor

Patients were divided by GTR into subgroups for the purpose of data analysis.

Defect (Sponsor Categories)	Number of patients
FC (Femoral Condyle)	74 (48%)
FC+ACL (Ant. Cruciate Lig. Repair)	23 (15%)
OCD (Osteochondritis Dissecans)	10 (7%)
Other	3 (2%)
Patella	22 (14%)
Patella+FC	16 (10%)
Tibia	5 (3%)
Total	153 (100%)

Sponsor Clinical Outcome

GTR assessed clinical outcome for each of 82 patients who answered the question "how does your knee feel now compared to before surgery?" Somewhat over 70% of all patients and over 70% of patients with only femoral condyle lesions reported that they had improved status.

Limitations of Sponsor Data Source

The questionnaire data measured a global outcome score at a single time point. Baseline data were not collected on patients, and detailed comparisons of patient outcomes following AuCC implantation to pre-treatment conditions were not possible. Data were incomplete; not all questions were answered by patients and not all patients who completed questionnaires were included in the database for analysis. Other procedures performed simultaneously at the time of AuCC implantation (e.g., anterior cruciate ligament repair) often confounded the data analysis, making the relative contribution of AuCC implantation to patient outcomes difficult to estimate.

Medical Reviewer Data Collection and Efficacy Analysis

Reviewers from the Agency collected additional data from primary records of all 153 patients treated in Sweden to supplement the sponsor's database and to perform independent analyses. The medical reviewers prospectively developed clinical outcome measures prior to an inspection trip to Sweden. All physician notes were made available to the medical reviewers during this inspection. Approximately 110 patients agreed to have their records translated into English. Copies of these records were provided to the

medical reviewers. The remaining patients had records which were available only in Swedish. These records, in accordance with Swedish law, were reviewed with the patient's identity concealed. The sponsor provided a translator and all of these additional records were translated orally for the medical reviewer, who took notes regarding the patient's treatment and outcome.

Definitions of Patient Outcomes

The patients were classified according to fixed objectives as defined below.

"Functional Outcome" This outcome measure is based on an assessment of the patient's symptoms and level of function after treatment with AuCC implantation compared to before treatment. Possible outcomes were: a) Resumed all activities, b) Some improvement, c) No improvement.

Patients who "Resumed all activities" were able to resume their pre-injury level of function without significant symptoms. Patients with "Some improvement" had apparent noticeable improvement of symptoms and function compared to pre-treatment levels but were not fully restored to their pre-injury status. This category contained a relatively wide range of possible function levels. For example, a patient whose pre-treatment function was restricted to walking with crutches might have a quite limited post-treatment status and still be categorized as "Some improvement" if the data showed this patient as noticeably better. Patients with "No improvement" were not noticeably improved compared with their status prior to AuCC implantation. This category includes patients whose status was worse than it had been prior to AuCC implantation.

"Objective Outcome" This outcome measure is based on an assessment of the structural integrity of the patient's cartilage repair as seen at arthroscopy or follow-up surgery. The reviewers defined possible outcomes as follows: a) Macroscopic integrity, b) Minor defects, c) Major defects.

Patients with cartilage showing filled defects without evidence of other structural aberrations were classified as having "Macroscopic integrity". "Macroscopic integrity" does not, however, imply that the tissue appeared normal or was necessarily of normal consistency, or that the cartilage tissue was restored to normal. Rather, it implies that the defect was filled without evidence of other structural problems. Patients with cartilage showing structural defects which were highly likely to imply a therapeutic failure for AuCC implantation (e.g. partial or complete loss or attachment of the repair tissue) were classified as having "Major defects", while patients with cartilage showing defects (e.g. partial filling of the defect, fissures or erosions in the repair tissue, surrounding hypertrophic tissue, etc.) were classified as having "Minor defects", which might not necessarily imply a

therapeutic failure (in the judgment of the medical reviewers). The "Major defects" category also included any patient whose repair tissue was completely removed by the surgeon when performing an additional follow-up procedure.

Medical Reviewer Procedure Groups

The medical reviewer divided patients into somewhat different groups than those of the sponsor, based on procedures performed, as defined below:

FC	Patients with a femoral condyle transplant and no other procedures
FC, O	Patients with a femoral condyle transplant and other procedures such as anterior cruciate ligament repair, but no patellar transplant or patellar debridement
FC, P, O	Patients with a femoral condyle transplant and a patellar transplant or debridement, with or without other procedures
Patella	Patients with a patella transplant, no femoral condyle transplant, and possibly other procedures (These patients often had other procedures to realign the patella)
OCD	Patients with a history of osteochondritis dissecans (These transplants were generally on the femoral condyle. They differ from FC patients, whose injuries were almost always related to trauma.)
Tibia	Patients with a tibial condyle transplant, with or without other procedures

The following table gives the tabulation of patient numbers by medical reviewer category.

Defect (Medical Reviewer Categories)	**Number of Patients**
FC group	50 (33%)
FC, other group	28 (18%)
FC, patella, other group	30 (20%)
OCD group	19 (12%)
Patella group	21 (14%)
Tibia group	5 (3%)
Total	153 (100%)

Functional Outcome at 2 years

In reviewing the primary data, the medical reviewers assessed the patient's functional outcome within the window of 22 to 28 months from surgery. This window was chosen to allow sufficient time for the effects of AuCC implantation therapy to become evident and to allow analysis of outcomes for a select group of patients at a relatively uniform time point. Many alternative therapies provide an initial response that is short-lived. Although the actual duration of such responses are variable, most do not persist for 2 years. If no patient follow-up visits occurred between 22 and 28 months, then the patient did not have an assessment of Functional Outcome at 2 years, with one exception. Any patient who had a "definitive failure" at an earlier time point was brought forward as a failure to the 22 month to 28 month window. (A diagnosis of "definitive failure" was made if there was no chance that the cartilage cell transplant could later prove successful, such as when a surgical resection of the entire transplant was performed during an alternative later procedure.)

The medical reviewers chose Functional Outcome at 2 years as an analysis to minimize the effects of variation in patient follow-up. Functional Outcome at 2 years was meant to capture one relatively uniform endpoint for all the patients included in this analysis. Patients must have been followed during the 22 month to 28 month window in order to be rated a success, but could fail at an earlier time point and still be included in the total failures at 22 to 28 months.

The following table represents the Medical Reviewer Functional Outcome at 2 years by Medical Reviewer Treatment Group:

Medical Reviewer Functional Outcome at 2 years
(22 to 28 Months)
by Medical Reviewer Treatment Group

	Resumed All Activities	Some Improvement	No Improvement	Unevaluable	Total
FC	2 (15%)	5 (38%)	5 (38%)	1 (8%)	13
FC,O	3 (33%)	5 (56%)	1 (11%)	0 (0%)	9
FC, P, O	1 (20%)	2 (40%)	2 (40%)	0 (0%)	5
Patella	2 (14%)	6 (43%)	6 (43%)	0 (0%)	14
OCD	6 (67%)	1 (11%)	2 (22%)	0 (0%)	9
Tibia	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1
Total	14(27%)	19 (37%)	17 (33%)	1 (2%)	51

All patients had assessments of their functional and objective outcomes at the last follow-up visit. Since the patients were not treated under a prospective protocol, there was wide variation among the patients regarding the spacing between follow-up visits and the duration of follow-up.

Functional Outcome at End of Follow-up

Functional outcome at the End of Follow-up is based on measurements of the functional outcome defined by patient symptoms and function at the end of follow-up. Patient follow-up in this series varied widely, with 26 of 153 (17%) patients having a follow-up less than 12 months, 72 (47%) between 12 and 23 months, 35 (23%) of 24 to 35 months, and 20 (13%) more than 36 months.

The reviewers assessed functional outcome of all patients who had 18 or more months of follow-up. This analysis complements that from Functional Outcome at 2 years, but is more influenced by variables which caused patients to end their follow-up.

The following table represents the Medical Reviewer Functional Outcome at End of Follow-up by Medical Reviewer Treatment Group for patients with 18 months of follow-up or greater:

Medical Reviewer Functional Outcome at End of Follow-up by Medical Reviewer Treatment Group (Patients with 18 or more months of Follow-up)

	Resumed All Activities	Some Improvement	No Improvement	Unevaluable	Total
FC	7 (27%)	8 (31%)	9 (35%)	2 (8%)	26
FC,O	4 (25%)	9 (56%)	3 (19%)	0 (0%)	16
FC, P, O	5 (42%)	7 (58%)	0 (0%)	0 (0%)	12
Patella	3 (17%)	7 (39%)	7 (39%)	1 (6%)	18
OCD	6 (50%)	4 (33%)	2 (17%)	0 (0%)	12
Tibia	0 (0%)	0 (0%)	2 (100%)	0 (0%)	2
Total	25(29%)	35 (41%)	23 (27%)	3 (3%)	86

As previously noted, the sponsor requested an indication for lesions of the femoral condyle. Information for such patients is contained in the first two rows of the above table. The table below summarizes the information for this group of patients.

	Resumed all activities	Some improvement	No improvement	Total
Femoral Condyle	7 (29%)	8 (33%)	9 (38%)	24
Femoral Condyle plus Other	4 (25%)	9 (56%)	3 (19%)	16
Total	11 (28%)	17 (42%)	12 (30%)	40

The functional outcomes at the end of follow-up and at 22 to 28 months, considered in light of the natural history and outcomes of other procedures reported in the literature, was taken to provide evidence suggesting that some patients had experienced clinical benefit.

Objective Outcome at End of Follow-up

This assessment measures patient outcome at the end of therapy based on the patient's objective data, (e.g. generated at arthroscopy). The patient's objective outcome final measurement in this category might not temporally correspond to the functional outcome at end of therapy, however, these two outcome measures tended to track together in time; i.e. if the patient was having clinical problems, further objective (e.g. arthroscopic) measurements were often made. Objective data could be unavailable (especially observed in the later patients) if the patient experienced clinical improvement following therapy with AuCC implantation. Patients without data were scored as "Unknown" for objective outcome. Estimates of patient objective outcome data therefore may underestimate the true benefits of AuCC implantation. Thus, objective outcome data should be considered supportive to the functional outcome data from functional outcomes.

The following table represents the medical reviewer objective outcome at end of follow-up by medical reviewer treatment group for patients with 18 months of follow-up or greater:

Medical Reviewer Objective Outcome
at End of Follow-up
by Medical Reviewer Treatment Group
(Patients with 18 or more months of Follow-up)

	Macroscopic Integrity	Minor Defects	Major Defects	Unknown	Total
FC	2 (8%)	13 (50%)	8 (31%)	3 (12%)	26
FC,O	1 (6%)	5 (31%)	5 (31%)	5 (31%)	16
FC, P, O	0 (0%)	7 (58%)	1 (8%)	4 (33%)	12
Patella	0 (0%)	13 (72%)	4 (22%)	1 (6%)	18
OCD	1 (8%)	8 (67%)	1 (8%)	2 (17%)	12
Tibia	0 (0%)	2 (100%)	0 (0%)	0 (0%)	2
Total	4 (5%)	48 (56%)	19 (22%)	15 (17%)	86

Comparison of objective outcome to functional outcome indicated that patients with "Macroscopic integrity" always "Resumed all activities" (4 patients). Patients with "Minor defects" showed "Some improvement" in half the patients (22 of 45), while the other half were evenly split between "Resumed all activities" and "No improvement". Finally, patients with "Major defects" showed "No improvement" 60% of the time (11 of 19), with almost all of the remaining having "Some improvement" (7 of 19).

Efficacy Analysis in Patients who Failed Earlier Procedures

As noted above, several procedures can lead to short-term benefit in patients with cartilage defects but rarely result in durable benefit. Many of the patients who received therapy with AuCC also received, as part of the AuCC treatment procedure, debridement and lavage. Since debridement and lavage per se can result in benefit for several months or longer, we sought to assess whether the cell therapy provided benefits beyond those attributable to the other treatments.

Thirty three patients had been treated with debridement (without AuCC) prior to receiving AuCC therapy and had failed by the time of AuCC therapy. The time between the debridement procedure and the procedure employing AuCC was taken as the time of follow-up following the debridement procedure. Of these 33 patients, 22 had a follow-up period

after AuCC which was at least as long as their follow-up period after debridement. Since the pre-AuCC baseline timepoint was identical with the end of follow-up for debridement alone for these patients, an outcome of "Some improvement" or "Resumed all activities" implies a better outcome persisting for a longer duration after AuCC treatment than had been observed after prior debridement. At the end of follow-up for AuCC, 5 of the 22 had a functional outcome of "Resumed all activities" and an additional 8 of 22 had a functional outcome of "Some improvement" compared with the end of follow-up for debridement (i.e., pre-AuCC).

This analysis involves only patients who had failed debridement; therefore a valid comparison of AuCC to debridement is not possible. However, with the assumption that a second debridement would not have provided more durable benefit than had the first, one can conclude that 13 of these 22 patients achieved outcomes after therapy with AuCC superior to the outcomes they would have received with debridement alone without cells.

Histologic Efficacy Analysis

Structural restoration of a symptomatic defect in femoral articular cartilage consists of filling the defect with hyaline cartilage which has a normal ultrastructure and a normal articular surface.

Of 22 consecutive patients with biopsies of the repair site one year or more after treatment, 7 patients had restoration of hyaline cartilage, 8 patients had mixed hyaline and fibrocartilage, and 7 patients had fibrocartilage. Clinical benefit did not correlate with restoration of hyaline cartilage in this small group of 22 patients.

Of the 7 patients with hyaline cartilage, 3 specimens had minimal to no defects. Of these 3, only 1 specimen had restoration of the articular surface, while the other 2 did not have the articular surface present on the slide due to poor technical preparation of the biopsy slides. With regard to functional outcomes, one of the three patients was rated "Resumed all activities" and the other two were rated "Some improvement". Of the 8 patients with mixed hyaline and fibrocartilage, 1 patient had a relatively intact hyaline portion of the biopsy, and had a functional rating of "Resumed all activities."

Medical Reviewer Safety Analysis

In the Swedish retrospective series clinical data were available for a total of 153 patients with follow-up from 1 week to 94 months, and 86 patients had at least 18 months of follow-up.

One patient death was noted and was ascribed to suicide. This patient had a clinical failure at 16 months. The entire transplant was resected at that point

and replaced with carbon fiber rods. The patient's suicide occurred much later and was considered unrelated to the AuCC implantation procedure.

Although most of the adverse reactions noted were consistent with post-surgical local reactions, tissue hypertrophy at the implantation site was noted frequently on arthroscopy and often was associated with clinical symptoms.

Of 86 patients with at least 18 months of follow-up from this series, 37 (43%) had hypertrophic tissue noted at follow-up arthroscopy. Many of these patients had clinical symptoms, including painful crepitations or "catching" associated with this hypertrophic tissue. These symptoms generally resolved after careful arthroscopic resection of the hypertrophic tissue. In about 10% of patients who had hypertrophic tissue arthroscopically resected, symptomatic hypertrophic tissue recurred, often repeatedly, after a 6 to 12 month symptom free interval. Additional arthroscopic resection of this tissue was then required.

Of 153 patients treated with AuCC implantation in Sweden, 34 (22%) of patients had adverse events other than hypertrophic tissue as follows: intra-articular adhesions, 8%; superficial wound infection, 3%; hypertrophic synovitis, 3%; post-op hematoma, 2%; adhesions of the bursa suprapatellaris, 2%; and hypertrophic synovium, 1%. About 1% of patients developed severe adhesions resulting in "frozen knee" and requiring lysis. Adverse reactions of less than 1% incidence included keloid-like scar, pannus formation, significant swelling of the joint, pain with post-op fever, and hematoma following routine arthroscopy.

2. U.S. Registry Data

The sponsor created a registry for US patients who were treated with Carticel™. The sponsor's stated intent in this registry is to capture clinical information on the outcomes of patients treated in the U.S. No arthroscopic or histological data are available in this group.

As of the most recent report submitted March 14, 1997, of 241 patients treated for a variety of cartilage defects, 191 patients had undergone repair of lesions in the femoral condyle. Of these 191 patients, 38 had at least 12 months of follow-up.

Patient outcomes were based on a modified Cincinnati Knee Rating System, scored from 1 to 10; 2 for Poor, 4 for Fair, 6 for Good, 8 for Very Good, and 10 for Excellent. A score of 10 signified no limitations, while a score of 8 signified only a few limitations with sports. Both clinicians and patients rated the outcomes. Of the 38 patients with 12 months of follow-up, 37 had ratings from both the clinician and the patient at baseline and at 12 months.

Efficacy Evaluation

In general, the clinicians rated the patient baseline from 2 to 4, although the patients rated their own baselines at 2 to 6. The medical reviewer tabulated all patients who achieved a 12 month score from 8 to 10 on both the clinician's and patient's outcome rating to create a category which might correspond with the reviewer's category of "Resumed all activities" in the Swedish series. Of the 37 patients, 11 (30%) achieved a 12 month score of 8 or higher. This outcome corresponds well with the medical reviewer ratings of "Resumed all activities" in the Swedish series.

The medical reviewer then created a category of patients who did not improve or improved a maximum of 1 point on either the clinician's or the patient's evaluation. Of the 37 patients, 7 (19%) could be categorized as a "No improvement" category.

Although follow-up times were more limited, functional outcomes in the U. S. registry data indicated patient functional outcomes following treatment with Carticel™ were consistent with those observed following AuCC implantation in Sweden.

Safety Evaluation

Of those 244 patients in the registry, 44 had twelve months of follow-up (38 with femoral condyle defects and 6 with other cartilage defects). Of those 44 patients with twelve months of follow-up, 6 (14%) patients had symptoms requiring arthroscopy and shaving of hypertrophic tissue. Considering that the follow-up was only 12 months, that routine arthroscopy was not part of the registry protocol, and that 5 of the 6 patients with symptomatic tissue hypertrophy required arthroscopy within 3 to 6 months, the registry confirmed the finding in the Swedish series that symptomatic tissue hypertrophy is an expected and relatively frequent side effect. Other adverse events in these patients included 2 (5%) with symptomatic intra-articular adhesions, and 1 (2%) with synovitis.

C. Summary

The basis for the efficacy determination involves three lines of evidence as noted above: functional outcomes compared with those reported in the literature, comparison of functional outcomes with those resulting from prior debridement alone in the same patients, and histological findings on biopsy. These lines of evidence are judged to meet the standards for accelerated approval under 21 CFR 601.41 applicable to some products for serious and life-threatening diseases. To substantiate long-term clinical benefit of Carticel™ implantation, GTR

has committed to two controlled post-marketing trials including a definitive study of the specific added value of the cells themselves; and an assessment of longer-term outcomes in controlled trials.

Carticel™ therapy appears safe based on experience to date. Collection of longer-term safety data will continue in the post-approval period.

VI. ADVISORY COMMITTEE MEETING

Data in support of the Carticel™ product made by Genzyme Tissue Repair were discussed at March 6, 1997 meeting of the Orthopedics and Rehabilitation Devices Advisory Committee. The committee indicated that the sponsor had demonstrated that the Carticel™ therapy procedure outcomes were reasonably likely to provide clinical benefit. The members identified a number of areas in which further data were needed and provided substantial input regarding design of clinical trials to obtain such data.

VII. RECOMMENDATIONS AND PHASE 4 COMMITMENTS

Under accelerated approval regulations, post-approval studies are required to confirm the long-term clinical benefit of this product and to assess the contribution of the autologous cells to observed benefit of the procedure.

A number of phase 4 commitments have been made by GTR to meet the requirements of accelerated approval under 21 CFR 601.41 and to further develop and validate manufacturing process and testing.

A. Clinical Commitments: The condition of accelerated approval will be met by completion of the clinical studies designed to do the following:

1. To establish the contribution of autologous cultured chondrocytes to structural and functional patient outcomes in a randomized, double-blind, placebo-controlled study of periosteal flap, with and without concomitant autologous cultured chondrocytes, in patients with femoral cartilage defects;

2. To verify that the observed short-term functional, structural and histological outcomes will lead to durable clinical benefit by studying long-term clinical outcomes in a randomized, open-label controlled, three-arm comparative study of Carticel™ administration with periosteal flap versus abrasion arthroplasty versus microfracture.

Design, initiation, accrual, completion, and reporting of these studies is expected to occur within the framework described in the letter of July 17, 1997 and as further clarified in the fascimile of August 22, 1997 to fulfill the requirements of accelerated approval, both studies must be conducted with due diligence and both must demonstrate superiority of the Carticel™ therapy over the comparator on primary efficacy outcomes.

Additional clinical commitments include:

3. To continue its current registry program and exercise due diligence in an effort to collect and report a minimum of 2 years post-implantation data including both efficacy and safety data on at least first 125 US patients.

4. To analyze and submit to the agency clinical outcome data gathered at 36 months follow-up on all patients enrolled in the open label phase 4 comparative study.

B. Manufacturing commitments: GTR has committed to continue development of Carticel™. These commitments include development of additional lot release criteria, validation of assays, and refinement of culture conditions. The specific commitments made by GTR for further development of the product and manufacturing facility prior to licensure are the following:

Product-Related Commitments:

1. To validate the chondrocyte morphology release test and to verify the identity of the various cell types seen in chondrocyte expansion cultures. Completion of all morphology testing is anticipated during the first Quarter of 1998;

2. To validate sample storage for, and the interchangeability of, the gel clot and kinetic chromogenic LAL assays in the testing of Autologous Cultured Chondrocytes. Completion of this testing is anticipated by September, 1997;

3. To develop a protocol and Standard Operating Procedure (SOP) for establishing and qualifying reference cell strains. Associated validation data and specifications are anticipated by January, 1998;

4. To develop and validate an identity assay using molecular markers specific for chondrocytes. Progress reports on the development of this assay are anticipated at six month intervals;

5. To establish objective criteria for expansion of previously frozen chondrocytes. Criteria and final manufacturing procedures are anticipated by January, 1998;

6. To develop data demonstrating the inability of infectious virus to replicate in chondrocyte cell cultures. Completion of this study is anticipated by January, 1998;

7. To validate product shelf life under a variety of shipping conditions. Progress reports are anticipated at six month intervals;

8. To develop and evaluate a serum-free medium for chondrocyte expansion. The first progress report is anticipated in January, 1998;

Establishment -Related Commitments:

1. To perform routine monitoring of air flow in the production cleanroom and to set air change specifications based on these data;

2. To conduct studies to demonstrate the effectiveness of disinfecting agents used in the product facility and on production equipment and containers.

VIII. AUXILLARY PRODUCTS

In addition to information and data supporting marketing of autologous cultured chondrocytes, the GTR biologics license application also included information on a biopsy transport kit which is used to transport cartilage biopsy from the clinical treatment site to GTR facilities. This kit, which is a medical device, was reviewed in this BLA and has been found appropriate for its labeled use.

IX. APPROVED PACKAGE INSERT

Copies of the Carticel™ approved package insert and the Cartilage Biopsy Transport Kit Directions for Use are attached.

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Autologous Cultured Chondrocytes
Licensed: August 22, 1997
Licensing Committee

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