ChondroCelect 10,000 cells/microlitre, implantation suspension
B/1 falcon tube with 1, 2 or 3 microtubes + 1 syringe + 18G venous catheter+ 2 6.0 vicryl sutures (CIP: 34009 577 381 8 1)

Applicant: TIGENIX NV

<table>
<thead>
<tr>
<th>INN</th>
<th>Autologous chondrocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (year)</td>
<td>M09AX02 (other drugs for disorders of the musculo-skeletal system)</td>
</tr>
<tr>
<td>Reason for the request</td>
<td>Inclusion</td>
</tr>
<tr>
<td>List(s) concerned</td>
<td>Hospital use (French Public Health Code L.5123-2)</td>
</tr>
<tr>
<td>Indication(s) concerned</td>
<td>“Repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults. Concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present. Demonstration of efficacy is based on a randomised controlled trial evaluating the efficacy of CHONDROCELECT in patients with lesions between 1 and 5 cm².”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Actual benefit</th>
<th>Insufficient AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in actual benefit</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Recommendations</td>
<td>Inclusion on the list of medicines approved for hospital use is not recommended</td>
</tr>
</tbody>
</table>

The legally binding text is the original French version
01 **ADMINISTRATIVE AND REGULATORY INFORMATION**

<table>
<thead>
<tr>
<th>Marketing Authorisation (centralised procedure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting date: 5/10/2009</td>
</tr>
<tr>
<td>This medicinal product is the subject of a risk management plan containing the risk minimisation plan with, in particular, follow-up of these risks (see appendix I):</td>
</tr>
<tr>
<td>- Potential major risks: Partial or complete delamination of the periosteal flap, synovitis, damage to the subchondral bone,</td>
</tr>
<tr>
<td>- Identified major risks: Symptomatic hypertrophy of the cartilage, swelling of the knee joint, crepitation of the knee joint, effusion of liquid in the joint, arthrofibrosis, inefficacy of the treatment (treatment failure),</td>
</tr>
<tr>
<td>- Missing information: Long-term durability of the repair; clinical data in patients with larger lesions (&gt; 4 cm²); confirmation of the clinical data in patients with smaller lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prescribing and dispensing conditions/special status</th>
</tr>
</thead>
<tbody>
<tr>
<td>List I</td>
</tr>
<tr>
<td>Medicinal product reserved for hospital use. Prescription restricted to certain specialists in orthopaedic surgery and traumatology.</td>
</tr>
<tr>
<td>Use of ChondroCelect will be restricted exclusively to hospitals meeting the criteria described in the RMP and the following requirements:</td>
</tr>
<tr>
<td>- prior specialised training for the surgical and auxiliary team;</td>
</tr>
<tr>
<td>- the written informed consent of each patient has been obtained;</td>
</tr>
<tr>
<td>- a strict logistic procedure;</td>
</tr>
<tr>
<td>- an individual patient rehabilitation programme;</td>
</tr>
<tr>
<td>- the selection of patients according to the target population defined.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATC Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
</tr>
<tr>
<td>M Musculo-skeletal system</td>
</tr>
<tr>
<td>M09AX Other drugs for disorders of the musculo-skeletal system</td>
</tr>
<tr>
<td>M09AX02 Chondrocytes, autologous</td>
</tr>
</tbody>
</table>

02 **BACKGROUND**

CHONDROCELECT (autologous chondrocytes) is the first cell therapy product approved as an innovative therapeutic medicinal product by the EMA which is available in France and can be used for autologous chondrocyte implantation (ACI). This proprietary medicinal product was first examined by the Transparency Committee in 2010 with a view to its inclusion; the Committee gave an opinion on 6 October 2010 in which it did not recommend reimbursement in the same indication; it stated that “Although the Committee believes this is an innovative biotechnology, the actual benefit of CHONDROCELECT must provisionally be regarded as insufficient, given the current data, to warrant its reimbursement. The Committee is unable to evaluate its therapeutic benefit, particularly in preventing the onset of osteoarthritis in the long term”.

This Opinion concerns a new request for inclusion submitted by the company.
03 THERAPEUTIC INDICATION

“Repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS]\(^1\) grade III or IV) in adults. Concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present. Demonstration of efficacy is based on the results of a randomised controlled trial evaluating the efficacy of CHONDROCELECT in patients with lesions between 1 and 5 cm\(^2\).”

04 DOSAGE

“Dosage
- The amount of cells to be administered is dependent on the size (surface in cm\(^2\)) of the cartilage defect. Each vial contains an individual treatment dose with a sufficient number of cells, obtained from a biopsy, to treat the lesion according to its size. The recommended dose is 0.8 to 1 million cells/cm\(^2\), corresponding to the use of 80 to 100 microlitres of suspension per cm\(^2\) of cartilage defect.
- Limited data are available on adult patients older than 50 years.
- Safety and efficacy in children and adolescents (aged less than 18 years) have not been established. CHONDROCELECT is therefore not recommended for use in children and adolescents below 18 years.

Conditions of use
- CHONDROCELECT must be used only by a trained and qualified surgeon, and it must be used only in a hospital setting.
- CHONDROCELECT is intended solely for use in autologous cartilage repair and is administered to patients in an Autologous Chondrocyte Implantation procedure (ACI). It must be used in conjunction with surgical debridement (preparation of the injured zone), physical suture of the lesion (insertion of a biological membrane, preferably a collagen membrane) and a programme of rehabilitation.
- In some cases it can be possible that the source chondrocytes of the patient are not expandable or that the release criteria are not met, due to poor biopsy quality, patient characteristics, or manufacturing failure. Therefore it can occur that CHONDROCELECT cannot be delivered. The surgeon will be informed as early in the process as possible, and should hence select an alternative treatment for the patient concerned.
- Concomitant knee problems like early osteoarthritis, osteochondritis dissecans, instability of the knee, cartilage lesions at locations other than the femoral condyle, lesions of knee ligaments or of the meniscus, varus or valgus malalignment (abnormal weight distribution in the knee) and inflammatory joint disease are potential complicating factors. In the pivotal study, patients with these comorbidities of the knee were excluded from treatment. Where possible, concomitant

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\(^1\) Cartilage lesions are ranked by the International Cartilage Repair Society (ICRS) in four grades according to their depth (descriptive arthroscopic analysis):
- grade I “nearly normal”: chondral softening or presence of fibrillations (grade Ia); if lacerations or superficial fissures are present (grade Ib);
- grade II “abnormal”: loss of substance less than 50% of chondral height;
- grade III “severely abnormal”: lesions of more than 50% of thickness which may reach the subchondral bone. A distinction is made between lesions which leave the calcified layer intact (grade IIIa) or cross it (grade IIIb), those affecting the subchondral layer (grade IIIc) and those rated as deep and destructive (grade IIIId);
- grade IV: osteochondral lesions (affecting the subchondral bone, affecting the superficial layer and impairing the bone surface).

Only symptomatic ICRS III and IV lesions require specific treatment (stimulation of the subchondral bone, multiple osteochondral grafts or grafts of chondrocytes) according to the ICRS.
knee problems should be corrected prior to or at the latest at the time of CHONDROCELECT implantation.

**Methods of administration**

- Local implantation is to be performed during arthrotomy under sterile conditions and requires both preparation of the site of the cartilage lesion and use of a biological membrane to keep the implanted cells in place. Complete joint haemostasis must be achieved prior to membrane fixation and cell implantation. In clinical studies with CHONDROCELECT a periosteal flap was used as biological membrane.

Scientific publications have shown that commercially available collagen membranes can be used as an alternative to the periosteal flap in ACI procedures.

However, CHONDROCELECT has not been evaluated in combination with this type of collagen membrane in clinical studies, although it has been used in patients treated with CHONDROCELECT under compassionate use. The safety data obtained in these patients do not indicate a particular concern, and confirm a lower incidence of hypertrophy as mentioned in the scientific literature comparing the use of collagen membranes and the periosteal flap.

- Fibrin glue is routinely used in ACI procedures to seal the outside margins and to improve the water-tightness of the compartment of the biological membrane used to cover the cartilage lesion. Fibrin sealant products differ significantly in their quantitative and qualitative composition. *In vitro* interaction studies were performed with a commercially available fibrin glue containing aprotinin (a fibrinolysis inhibitor of bovine origin). No interaction studies with any other type of fibrin glue were performed. However, the concomitant use of currently marketed fibrin glue with a synthetic fibrinolysis inhibitor (tranexamic acid) in the pivotal clinical trial did not reveal any safety concern.

- Implantation must be followed by an appropriate rehabilitation schedule lasting about one year. Its main objective is to avoid early damage which could lead to implant failure."
Isolated, unipolar loss of chondral substance in the knee with no associated ligament lesion in a weight-bearing area in young patients is a therapeutic problem. These cartilage lesions, which are most often traumatic in origin, are in most cases irreversible because of the low spontaneous repair capacity of cartilage versus hyaline cartilage. The current professional consensus, in the absence of any certainty about their natural history, is that these lesions are likely to progress to osteoarthritis in the long term.

The prevalence and incidence of isolated loss of chondral substance are not known. Conservative treatment can be offered to patients; these treatments, and in particular rehabilitation, are functionally effective in the management of gonarthrosis.

Several surgical techniques can also be offered, depending on the nature, size and depth of the lesion and the patient’s expectations:
- conservative or palliative surgery (arthroscopic lavage, debridement),
- repair surgery (drilling of the subchondral bone, abrasion, implantation of a membrane or matrix (AMIC), microfractures),
- prosthetic surgery (uncompartmental knee prosthesis), an option for bipolar or osteochondral lesions,
- restorative surgery (mosaicplasty, osteochondral allograft, autologous implant of chondrocytes or autologous chondrocyte implantation),

None of the current surgical techniques has demonstrated its efficacy in clinical criteria or its superiority by comparison with the other available surgical techniques.

The implantation of autologous chondrocytes is the most recent treatment option, since the first clinical publications are from 1994. ChondroCelect (autologous chondrocyte) is the first cell therapy medicinal product with Marketing Authorization to be supplied in France and can be used in this setting for ACI.

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2 Assessment of autologous chondrocyte implantation in the knee – interim report – HAS 2005
06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

CHONDROCELECT is the only medicinal product indicated in the “repair of single symptomatic cartilage defects (ICRS grade III or IV) of the femoral condyles of the knee in adults”. CHONDROCELECT, suspension of autologous cells, is intended to be used in restorative surgery with ACI.

06.2 Other health technologies

The other implantation techniques used in restorative surgery are:
- mosaic of multiple osteochondral autografts: mosaicplasty,
- osteochondral allograft
- allograft of chondrocytes or autologous chondrocyte or stem cell implantation.

The other surgical techniques that can be considered for treating cartilage lesions are:

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Objective</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative or palliative surgery</td>
<td>Elimination of microscopic debris</td>
<td>- Arthroscopic lavage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Debridement</td>
</tr>
<tr>
<td>Repair surgery</td>
<td>Formation of fibrocartilage by stimulation of stem cells of subchondral bone marrow</td>
<td>- Drilling of the subchondral bone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Abrasion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Implantation of membrane or matrix (AMIC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Microfractures</td>
</tr>
</tbody>
</table>

Finally, a unicompartimental knee prosthesis can ultimately be offered to certain patients. The only techniques reimbursed by National Health Insurance are:
- “cleaning of the knee joint, by arthroscopy” (NFJC001),
- “cleaning of the knee joint, by arthrotomy” (NFJC001),
- implantation of a knee prosthesis (NFKA006: Replacement of the knee joint with a unicompartimental femorotibial or femoropatellar prosthesis; NFKA009: Replacement of the knee joint with a fixed-hinge or rotatory prosthesis).

The prescription and administration of CHONDROCELECT necessitates the performance of a diagnostic and therapeutic procedure and the use of a medical device (fibrin glue, sutures, or collagen membrane as specified by the SPC for CHONDROCELECT) by a healthcare professional. The procedure for the in situ administration of CHONDROCELECT is not included in the Common Classification of Medical Procedures (CCAM). The collagen membrane intended to cover traumatic cartilage lesions that can be used for the in-situ administration of CHONDROCELECT is not covered.

Conclusion

The comparators mentioned are all clinically relevant except for the knee prosthesis.
### 07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

<table>
<thead>
<tr>
<th>Country</th>
<th>YES/NO</th>
<th>REIMBURSEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Yes</td>
<td>May 2011: Reimbursement by agreement, allowing use by centres of excellence, in a population of target patients, within strict budgetary limits. Agreement coupled with a standard “risk sharing” agreement in case the treatment fails.</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Yes</td>
<td>June 2012: Decision taken by the Dutch authority (NZa) to reimburse CHONDROCELECT; in accordance with the list of medicines reimbursable in a hospital setting.</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td>“Case by case” reimbursement after negotiation between the hospital and the appropriate regional health insurance scheme.</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Yes/no</td>
<td>Reimbursable only by certain private insurers Not reimbursed by the NHS</td>
</tr>
<tr>
<td>Spain</td>
<td>In progress</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>No</td>
<td>After analysing the methods of the pivotal study for the Marketing Authorisation dossier, the FDA (on 15 March 2010) asked for an additional “confirmation” study to be carried out before the BLA (Biologic License Application) authorisation procedure could be implemented. In this context, a pivotal study was proposed by the company (2012).</td>
</tr>
</tbody>
</table>

### 08 SUMMARY OF PREVIOUS ASSESSMENTS

<table>
<thead>
<tr>
<th>Date of opinion (reason for request)</th>
<th>6 October 2010 (Inclusion on the list of medicines approved for hospital use)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Repair of single symptomatic cartilage lesions of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults.</td>
</tr>
<tr>
<td><strong>AB (wording)</strong></td>
<td>Although the Committee believes that it is an innovative biotechnology, the actual benefit of CHONDROCELECT must provisionally be regarded as insufficient to justify its reimbursement, given the current state of the data. The Committee is unable to evaluate its therapeutic benefit, particularly in preventing the onset of osteoarthritis in the long term.</td>
</tr>
<tr>
<td><strong>IAB (wording)</strong></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
09 ANALYSIS OF AVAILABLE DATA

The assessment of the efficacy and safety of CHONDROCELECT is based on a phase III study (TIG/ACT/01&EXT/2000) and its open extension phase, the objective of which was to compare the efficacy of CHONDROCELECT with microfractures in terms of structural repair at 12 months. The data available at 12 (Saris 2008\(^3\)) and 36 months (Saris 2009\(^4\)) had already been submitted with the first application; the present dossier also contains the 60-month data.

The company also submitted the results of analyses of subgroups defined *a posteriori* (post-hoc analyses) and in particular of subgroups of patients defined according to the age of their lesions (greater or less than 3 years) (Vanlauwe 2011\(^5\)). Given the methodology of these analyses, the results can be considered only on an exploratory basis.

In its first submission, the company had also submitted a study of a compassionate use programme which has now been published with more recent data (Vanlauwe 2012\(^6\)).

The company has also supplied new data based on a literature review on the long-term clinical consequences of chondrocyte implantation used in cartilage repair (10 studies): a randomised clinical study (Bentley 2012), four group follow-ups (Corpus 2012, Moradi 2012, Viste 2012, Bhosale 2009), four case series (Peterson 2010, Beris 2012, Moseley 2012, Loken 2009) and one study on the benefit of MRI (Vasiliadis 2010).

Only the randomised clinical study and the long-term group follow-ups will be discussed in this Opinion.

09.1 Efficacy

9.1.1 Comparative studies

**ACI versus microfracture:** Study TIG/ACT/01&EXT/2000

Objectives of the study:
The study had two phases:
- a first 12-month open, comparative phase,
- a second 48-month open, comparative extension phase.

The objective of the first phase of the study was to demonstrate the superiority of ACI with CHONDROCELECT by comparison with microfracture in terms of the quality of the structural repair at 12 months as assessed by MRI.

If superiority was demonstrated, the second objective was to demonstrate the non-inferiority of the two techniques using the clinical signs and symptoms measured in terms of the change by comparison with the value on inclusion for the mean overall KOOS score at 12 and 18 months; non-inferiority was accepted if the lower limit of the 95% confidence interval did not exceed -9%.

This endpoint was added during the study at the request of the EMA.

The objective of the open extension phase was to assess, at each visit, the clinical superiority of CHONDROCELECT by comparison with microfracture in terms of the clinical criteria of the KOOS

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scale (assessing pain, certain symptoms such as swelling and stiffness of the joint, activities of daily living, sporting activities and quality of life) and treatment failures (with two analyses scheduled for 36 and 60 months).

Methodology: Randomised, single-blind phase III study (the clinical, histopathological and histo-morphological assessors did not know what treatment had been assigned), comparing ACI using CHONDROCELECT with microfracture, performed in 112 patients with single symptomatic cartilage lesions (ICRS grade III or IV) of the femoral condyle with a surface area of between 1 and 5 cm².

Inclusion criteria: Patients who were over 18 years to 50 years of age with single symptomatic cartilage lesions of the femoral condyle of 1 to 5 cm² and:
- who were actively participating in the rehabilitation programme in the follow-up programme;
- who could receive only treatment with paracetamol as monotherapy or in combination with an NSAID (maximum dose of 4 g/day) and stopped their treatment with paracetamol as monotherapy or in combination with an NSAID within 2 weeks before the initial visit and the follow-up visits in the 8th week and in the 3rd, 6th, 9th and 12th month after surgery.

Non-inclusion criteria, in particular:
- presence of a clinically relevant lesion of the patellar cartilage,
- presence of a lesion of the cartilage in the femoropatellar joint,
- dissecting osteochondritis or subchondral sclerosis,
- advanced osteoarthritis,
- instability of the knee ligaments,
- history of meniscal transplantation or suture.

Treatments:
- CHONDROCELECT (0.8 and 1 × 10⁶ cells/cm²) under periosteal flap, n = 51,
- Microfractures, n = 61.

In the CHONDROCELECT group a sample of cells was taken by arthroscopy and they were first developed in vitro. Patients were then hospitalised 4 weeks later so that CHONDROCELECT could be administered to them by arthrotomy. The microfractures, by contrast, were carried out in a single session on assessment of the lesion by arthroscopy.

Primary efficacy endpoints:
- change in the mean sum of the histomorphometry scores for staining with safranin O and H&E and with anti-collagen II antibodies (sum of the two ratios) at 12 months¹.
- change, by comparison with the value on inclusion, in the mean overall KOOS score (Knee Osteoarthritis Outcome)⁷ not taking account of results for sporting and leisure activities, at 12 and 18 months.
- mean change in the ICRS II overall histological assessment score at 12 months.

Given that there is no established long-term correlation between the histological results and any clinical benefit, the initially defined primary efficacy endpoint (overall histomorphometry and histology score) was changed during the study at the request of the regulatory authorities⁸; other histological rating scales were used (ICRS II) and a clinical endpoint was added by measuring the overall KOOS score.

Note: The calculation of the number of subjects needed was based on a 60% improvement in the histological and histomorphometric parameters (MODS score) in patients treated with CHONDROCELECT with a power of 90% and a one-sided risk of 2.5% and not on the new endpoints (ICRS II histological score and clinical endpoint) used to read the results.

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¹ The KOOS scale is based on a self-completion questionnaire covering five areas, each evaluated using the Likert scale graduated from 1 to 5: pain, other symptoms such as joint swelling and stiffness, activities of daily living, sporting and leisure activities and quality of life.
² CHMP Scientific advice; EME/1519996/2006
Long-term endpoints (follow-up phase), in particular:
- change by comparison with the value on inclusion for the mean overall KOOS score at 36 and 60 months.
- responder rate (change on the VAS) and time to failure (defined as withdrawal of the implant or non-implantation).

RESULTS: See Table 1 (FAS population)
The patients’ characteristics were comparable on inclusion. Most of the patients included were less than 40 years old (70%).

Results for the primary efficacy endpoints:

**Table 1: Results for the primary efficacy endpoints (FAS population) at 12 months**

<table>
<thead>
<tr>
<th></th>
<th>CHONDROCELECT (n = 51)</th>
<th>Microfracture (n = 61)</th>
<th>Difference 95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural repair</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean sum of the ratios at 12 months (SD) – histomorphometric scores</td>
<td>n = 47</td>
<td>0.93 (0.41)</td>
<td>n = 54</td>
<td>0.67 (0.47)</td>
</tr>
<tr>
<td><strong>Histological evaluation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in overall ICRS II at 12 months by comparison with on inclusion</td>
<td>n = 36</td>
<td>48.63 (23.92)</td>
<td>n = 46</td>
<td>37.76 (21.85)</td>
</tr>
<tr>
<td><strong>Clinical evaluation (non-inferiority)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in the overall KOOS score at 12 months by comparison with on inclusion</td>
<td>n = 51</td>
<td>16.18 (2.42)</td>
<td>n = 58</td>
<td>14.37 (2.35)</td>
</tr>
</tbody>
</table>

After 12 months, the structural repair evaluated on the basis of the sum of the histomorphometric (staining with safranin O and H&E and coll II) and histological scores (the primary efficacy endpoint defined initially) had improved significantly with CHONDROCELECT under a periosteal flap by comparison with microfractures: difference 0.27 [0.09; 0.44], p = 0.003.

In contrast, after 12 months of treatment, the ICRS II histological evaluation score (primary efficacy endpoint added after amendment), evaluated in only 82/122 patients (73%), showed no statistical difference between CHONDROCELECT under periosteal flap and microfractures: difference 12.98 [2.93; 23.04], NS.

Finally, since the lower limit of the 95% confidence interval did not exceed -9% (difference 1.81, 95% CI [-3.28; 6.90]), the non-inferiority of CHONDROCELECT under periosteal flap by comparison with microfractures was demonstrated (intention to treat analysis) in terms of clinical efficacy evaluated on the overall KOOS scale (primary efficacy endpoint added after amendment); the per-protocol analysis is not available.

Results for long-term endpoints:
After 36 months of treatment, no significant difference was observed in terms of clinical efficacy on the overall KOOS scale between ACI using CHONDROCELECT with periosteal flap and the microfracture technique: 23.65 (4.24) versus 19.16 (4.35), difference 4.50 [-1.95; 10.94], NS. Similarly, no difference was observed at 60 months: 24.17 (5.57) versus 19.50 (5.40), difference 4.67 [-1.69; 11.03], NS.
The responder rate (change on the VAS\(^9\),\(^{10}\)) observed at 36 and 60 months is summarised in Table 2 below:

### Table 2: Responder rate at 36 and 60 months (change in the VAS)

<table>
<thead>
<tr>
<th></th>
<th>CHONDROCELECT</th>
<th>Microfracture</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>36 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>41</td>
<td>50</td>
</tr>
<tr>
<td>Worsening</td>
<td>2 (4.9%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Absence of clinical change</td>
<td>5 (12%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Responders</td>
<td>34 (83%)</td>
<td>33 (66%)</td>
</tr>
<tr>
<td><strong>60 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>Worsening</td>
<td>4 (9.3%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Absence of clinical change</td>
<td>12 (28%)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Responders</td>
<td>27 (63%)</td>
<td>31 (62%)</td>
</tr>
</tbody>
</table>

The percentage of responders did not differ between the groups at 36 and 60 months; this percentage was numerically higher in the CHONDROCELECT group than in the microfracture group at 36 months, but declined progressively over time (60 months).

At 60 months, the number of treatment failures (defined by withdrawal of the implant or non implantation) was not significantly different between the groups: seven in the CHONDROCELECT group versus 10 in the microfracture group, NS.

**Post-hoc analysis (subgroups defined a posteriori):**

- **Subgroup of patients defined according to the age of their lesions (greater than or less than 3 years)**
  
  This subgroup analysis was performed in 93/118 (80%) of the patients included in the study: 59 with lesions less than 3 years old (50% of patients included) and 34 more than 3 years old (29% of patients included).
  
  At 36 months, a difference was observed in terms of clinical efficacy, evaluated on the overall KOOS scale, between ACI with CHONDROCELECT and periosteal flap and the microfracture technique, only in patients with lesions less than 3 years old: 25.79 (3.70) versus 14.68 (3.40), difference 8.99 [0.01; 17.97], \(p=0.049\).
  
  This difference was also observed after 60 months: 9.84 [0.96; 18.71], \(p<0.05\).

  Since the analysis of the primary efficacy endpoint for the overall study population did not show any significant difference between ACI with CHONDROCELECT and periosteal flap and the microfracture technique and, given the methodology of that analysis (subgroup defined \textit{a posteriori}, using a small number of patients), the results must be seen as being only exploratory and must be confirmed in randomised clinical studies.

- **In the other subgroups studied (demographic parameters, size of the cartilage lesion, quantity of cells administered, etc.)** no difference was found.

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\(^9\) Worsening = patients with an increase in VAS pain of at least 20% and/or a worsening in the severity of the knee disorder by at least one category  
\(^{10}\) Responders = patients with a reduction in VAS pain of at least 20% and/or an improvement in the severity of the knee disorder by at least one category
**CACI versus mosaicplasty:** Bentley 2012\(^{11}\)

This randomised study compared the efficacy of ACI (autologous chondrocyte implantation) with that of mosaicplasty (multiple, mosaic osteochondral autografts) in 100 patients with a single cartilage lesion of the knee, associated with persistent pain and a lack of stability, who were followed up for at least 10 years. The mean size of the lesions on inclusion was 440.9 mm\(^2\) [100; 1050] in the ACI group and 399.6 mm\(^2\) [100; 2000] in the mosaicplasty group. Patients were randomised to two groups (58 to the ACI group and 42 to the mosaicplasty group) and both groups received identical postoperative rehabilitation.

Treatment failure (primary efficacy endpoint), defined as rejection of the implant shown by arthroscopy or review surgery, was less common in the ACI group than in the mosaicplasty group, 17\% versus 55\%; \(p<0.001\).

These results are difficult to interpret. In fact, firstly the distribution of cartilage lesion surface areas and their aetiology differed between the two groups which poses a problem in that these two factors may influence the efficacy of the techniques used. Secondly, two different techniques were used for the chondrocyte implant (collagen membrane and periosteal flap) and the proportion of patients who received each of these techniques is not known. Finally, the quantity of chondrocytes actually implanted in each of the patients is not known; thus, adherence to the dosage validated by the Marketing Authorisation for CHONDROCELECT cannot be guaranteed.

### 9.1.2 Group follow-up

**Corpus 2012\(^{12}\):**

In this before-after retrospective study, 29 patients in whom ACI of the knee had been carried out were followed up for at least 7 years. After mean follow-up for 8.4 years [7.14; 10.88] a statistically significant improvement in the scores on the different functional and symptomatic evaluation scales (IKDC, KOOS, Tygner-Lysholm LS scale, SF-12) was observed by comparison with the patients’ condition before surgical treatment.

**Moradi 2012\(^{13}\):**

In this before-after retrospective study, 23 patients in whom ACI of the knee had been carried out were followed up for at least 7 years. After follow-up for one year, a statistically significant improvement in the scores on the different functional and symptomatic evaluation scales (IKDC, LS, SF-36, TAS–Tegner activity score) was observed by comparison with the patients’ condition before surgical treatment. This improvement was observed after a mean follow-up period of 9.9 years even though a slight deterioration was observed over time.

Clinical follow-up by MRI was also used to evaluate tissue repair postoperatively; a complete lack of filling was observed in 52.3\% of the patients followed up.

**Viste 2012\(^{14}\):**

In this before-after study, 14 patients were included prospectively in a 6-year follow-up after knee ACI was performed. After 6 years’ follow-up, a statistically significant improvement in the functional and symptomatic evaluation score (IKDC) and a reduction in the VAS score for pain was observed in 12/14 patients. In two patients, no improvement was observed.

**Bhosale 2009\(^{15}\):**

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\(^{13}\) Moradi et al. First generation autologous chondrocyte implantation in patients with cartilage defects of the knee: 7 to 14 years clinical and magnetic resonance imaging follow-up evaluation. The Journal of Arthroscopic and Related Surgery 2012;28:1851-61

A total of 80 patients in whom knee ACI had been performed were evaluated as part of a retrospective before-after study. After a mean follow-up period of 5 years [2.7; 9.3], a statistically significant improvement in the functional and symptomatic evaluation score (Tygner-Lysholm) was observed in 81% patients by comparison with their condition before surgical treatment. In the other patients a deterioration was observed.

Given the methodology of these studies (group follow-ups) and the fact that the implantation of chondrocytes was not done using CHONDROCELECT, these results are poorly transferable.

9.1.3 Compassionate use programme

A compassionate use programme was run within the context of the Marketing Authorisation. This was an open, multicentre, non-interventional study performed between 2004 and 2008 at 43 European centres; data are available for 370 patients.

Characteristics of the patients included: patients with cartilage lesions of the knee for whom other treatments had not been effective and/or for whom there were no other treatment options. In April 2007, following discussions with the EMA, the patients to be included were specified:

- patients over 18 years of age,
- exclusion of subjects with osteoarthritis or advanced dissecting osteochondritis.
- In addition, surgeons were informed that CHONDROCELECT was intended to treat simple, symptomatic lesions of the femoral condyle in ICRS grade III or IV.

Characteristics of the lesions:
- Localisation: condylar (65.8%), patellar (19.2%), trochlear (8.9%), tibial (3.0%).
- Size: 0.25 to 20.0 cm², median 3.0 cm².
- Type: simple (85.4%), 2 lesions (11.4%), 3 lesions (2.7%), 4 lesions in four patients.

Efficacy was evaluated on the basis of a Clinical Global Impression (CGI) scale in terms of the effect observed (CGI effect) and the improvement (CGI improvement) and only a descriptive statistical analysis was carried out.

The effect was major in 39.2% of patients (n=107), moderate in 37.4% (102), minimal in 12.1% (33) and zero or worse in 11.3% (31).

An “improvement” was observed in 86.5% of patients (138), no change was observed in 7.3% of patients (20) and worsening was observed in 6.2% (17).

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16 CGI effect: Therapeutic effect: 4 levels, major, moderate, minimal, zero or deterioration.
17 CGI improvement: 8 levels 0 – Not evaluated, 1 – Very much improved, 2 – Much improved, 3 – Slightly improved, 4 – No change, 5 – Slightly worse, 6 – Much worse, 7 – Very much worse.
09.2 Adverse effects

9.2.1 Data from clinical studies

In study TIG/ACT/01&EXT/2000, adverse effects were observed in 42/51 patients (82%) in the CHONDROCELECT and 38/61 patients in the microfracture group. The commonest adverse effects (>10%) are summarised in the table below.

<table>
<thead>
<tr>
<th></th>
<th>CHONDROCELECT</th>
<th>Microfractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>25 (49%)</td>
<td>25 (41%)</td>
</tr>
<tr>
<td>Cartilage hypertrophy</td>
<td>14 (27%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Joint crepitation</td>
<td>10 (20%)</td>
<td>2 (3.3%)</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>7 (14%)</td>
<td>3 (4.9%)</td>
</tr>
<tr>
<td>Joint effusion</td>
<td>6 (12%)</td>
<td>3 (4.9%)</td>
</tr>
</tbody>
</table>

9.2.2 Data from the compassionate use programme

In this programme, adverse effect data are available for 370 patients treated with CHONDROCELECT. The adverse effects most commonly found were: knee pain (23.8%), arthritic effusion (8.5%), joint swelling (8.2%), joint crepitation (6.1%), muscular atrophy (6.1%) and limitation of movement (5.7%).

9.2.3 PSUR data

Since 5 October 2009, CHONDROCELECT has been used in 241 patients in five countries in which it is marketed.
Five pharmacovigilance reports (PSUR) covering the period between 5/10/2009 and 4/05/2012 are available. During this period, no serious or unexpected adverse effects were observed.

9.2.4 SPC data

According to the SPC, “adverse reactions occurred in 78.4% of patients over a 36-month postoperative follow-up period. The most common adverse reactions were arthralgia (47.1%), cartilage hypertrophy (27.4%), joint crepitation (17.6%) and joint swelling (13.7%). Adverse reactions collected from 370 patients included in a compassionate use programme are similar to those reported in the target population.
Most of the reported adverse reactions were expected as they were linked to the open-knee surgical procedure. The most common reactions reported immediately after surgery were joint swelling, arthralgia and fever. These were generally moderate and disappeared in the weeks following surgery.”
09.3 Summary & discussion

The evaluation of the efficacy and safety of CHONDROCELECT is based mainly on a 12-month single-blind, randomised study (TIG/ACT/01&EXT/2000) and its 48-month open extension phase, the aim of which was to compare ACI using CHONDROCELECT under a periosteal flap with microfractures in terms of the structural repair at 12 months and clinical efficacy at 12, 36 and 60 months.

The dossier also contains data from a compassionate use programme and a literature review on the long-term clinical consequences of the implantation of chondrocytes used in the context of cartilage repair (nine studies).

Main efficacy results

Randomised study versus microfractures, TIG/ACT/01&EXT/2000:

After 12 months, the results are contradictory in terms of the change in the structural repairs:
- CHONDROCELECT is superior to microfractures in the sum of the histomorphometric (staining with safranin O and H&E and coll II) and histological scores (initially defined primary efficacy endpoint): difference 0.27 [0.09; 0.44], p = 0.003.
- CHONDROCELECT is no different from microfractures as regards the ICRS II histological evaluation score (primary efficacy endpoint added after amendment): difference 12.98 [2.93; 23.04], NS.

From a clinical point of view,
- After 12 months, only the non-inferiority of CHONDROCELECT by comparison with microfractures was demonstrated (intention to treat analysis) on the overall KOOS score (primary efficacy endpoint added after amendment); the per-protocol analysis is not available.
- After 36 and 60 months of treatment, CHONDROCELECT is no different from microfractures in terms of clinical efficacy evaluated on the overall KOOS scale. Similarly, the percentage of responders (lack of recurrence) did not differ between the two groups, either after 36 months of treatment (83% vs 66%) or after 60 months (63% vs 62%).

Analyses of subgroups defined a posteriori were carried out. Since the analysis of the primary efficacy endpoint for the overall study population did not show any significant difference between ACI with CHONDROCELECT and periosteal flap and the microfracture technique, and given the methodology of these analyses (subgroups defined a posteriori, using a small number of patients), the results must be seen as being only exploratory and must be confirmed in randomised clinical studies.

Randomised trial (Bentley 2012) comparing ACI (autologous chondrocyte implantation) with mosaicplasty (multiple osteochondral autografts in a mosaic pattern) performed in 100 patients. Treatment failures (implant rejection shown by arthroscopy or review surgery) was less common after ACI than after mosaicplasty: 17% versus 55%, p < 0.001.

These results are difficult to interpret. In fact, firstly, the distribution of the cartilage lesion surfaces and their aetiology differ between the two groups which poses a problem in that these two factors may influence the efficacy of the techniques used. Secondly, two different techniques were used for the chondrocyte implant (collagen membrane and periosteal flap) and the proportion of patients who received each of these techniques is not known. Finally, the quantity of chondrocytes actually implanted in each of the patients is not known; thus, adherence to the dosage validated by the Marketing Authorisation for CHONDROCELECT cannot be guaranteed.

Group follow-ups:
The four studies available show an improvement in the different functional and symptomatic evaluation scores in patients treated with chondrocyte implantation. However, given the non-comparative nature of these studies and the fact that the implantation techniques used did not use CHONDROCELECT, these results are poorly transferable.
Compassionate use programme:
In the 370 patients treated at 43 European centres, the effect was major in 39.2% of the patients, moderate in 37.4%, minimal in 12.1% and zero or worse in 11.3%. An improvement was observed in 86.5% of patients, no change was observed in 7.3% and deterioration was observed in 6.2%.

Main safety results
In the study versus microfractures the local effects were more common after CHONDROCELECT than after microfractures: arthralgia (49% vs 41%), cartilage hypertrophy (27% vs 11%), joint crepitition (20% vs 3.3%), joint swelling (14% vs 4.9%), articular effusion (12% vs 4.9%).

According to the SPC, “adverse reactions occurred in 78.4% of patients over a 36-month postoperative follow-up period. The most common adverse reactions were arthralgia (47.1%), cartilage hypertrophy (27.4%), joint crepitation (17.6%) and joint swelling (13.7%). Most of the adverse reactions reported were expected as they were linked to the open-knee surgical procedure. The most common reactions reported immediately after surgery were joint swelling, arthralgia and fever. These were generally moderate and disappeared in the weeks following surgery.”

Main points of discussion and missing data
The main initial objective of study TIG/ACT/001/2000 was to demonstrate the superiority of CHONDROCELECT in structural repair at 12 months by comparison with the microfracture technique. The choice of a “histological” endpoint without a clinical endpoint is very debatable because there is no long-term correlation between the histological results and any clinical benefit. Consequently, the primary efficacy endpoint of the study was changed during the study at the request of the regulatory authorities; other histological rating scales were used (ICRS II) and a clinical endpoint was added by measuring the overall KOOS score.

At 12 months the histological results are contradictory, depending on the score used (histo-morphometry score of ICRS II) and the clinical applicability of the histological results is hypothetical since the conclusion of the clinical data is the non-inferiority of the two techniques, using just an intention to treat analysis.

No data are available on the use of CHONDROCELECT with the collagen membranes currently marketed which can be used as an alternative to the periosteal flap in ACI techniques.

In terms of safety, comparative data are available only versus microfractures; no comparative safety data versus other surgical techniques are currently available.

In the absence of data, the therapeutic benefit of CHONDROCELECT in the long-term prevention of osteoarthritis has not been established.
Summary
The robustness of the efficacy results is debatable: a single pivotal study of non-inferiority with a limited population and the lack of demonstration of clinical superiority vis-à-vis microfracture with additional constraints in terms of the organisation of health care which are more severe with CHONDROCELECT. In fact, carrying out an autologous chondrocyte implant involves at least two hospitalisations, one for performing biopsies by arthroscopy, the other to implant the cells by arthrotomy. Attachment of the periosteal flap must be carried out by experienced surgeons by suturing the periphery of the cartilage, which is difficult to do and its durability is uncertain. The use of a collagen membrane should simplify the procedure by avoiding the suture of the periosteal flap, but no data on chondrocyte implantation based on use of this membrane have been supplied.

This chondrocyte implant technique is marked by a larger number of adverse effects than the microfracture, which could hamper or delay patient rehabilitation.

The new data available since the first examination by the Committee (60-month data from the pivotal study and a literature search) provide longer-term information but are no more demonstrative of the efficacy of CHONDROCELECT versus microfractures. In addition, the results from the analyses of subgroups defined a posteriori can be regarded as merely exploratory and will have to be confirmed in randomised clinical studies.

Finally, the Committee regrets the absence of any demonstrative clinical data on the change in the lesion and on its long-term functional consequences.

In the study versus microfractures these local effects were more common after CHONDROCELECT than after microfractures: arthralgia (49% vs 41%), cartilage hypertrophy (27% vs 11%), joint crepitation (20% vs 3.3%), joint swelling (14% vs 4.9%), articular effusion (12% vs 4.9%); there are no data comparing the safety of CHONDROCELECT with that of other surgical techniques. Although the adverse effects observed are not serious, they are very common and may potentially jeopardise the benefit of this more radical surgery to a greater extent than the comparison technique, given their nature, localisation and potential impact on patient rehabilitation.

A confirmatory study with a good level of evidence therefore seems essential.

09.4 Programme of studies
TiGenix gave an undertaking to the EMA to follow up patients treated during the marketing of CHONDROCELECT by means of an observational study lasting 36 months which is currently in progress in Belgium and the Netherlands.

Depending on the reimbursement situation in other countries, the protocol can be adapted to each country.

The consensus view is that surgical treatment is possible only for symptomatic knee cartilage lesions of grades III and IV\textsuperscript{21} in the ICRS arthroscopic classification.\textsuperscript{22}

The surgical technique chosen should make it possible to restore the hyaline cartilage by the least invasive means possible without compromising the ability to carry out another surgical intervention if it fails. The short- and medium-term therapeutic objectives are to repair the damaged cartilage by obtaining newly formed functional tissue, and to improve functional performance and the patient’s quality of life. The long-term objective is to prevent gonarthrosis.

Several surgical techniques can be offered, depending on the nature and size of the lesion and the patient’s expectations:
- conservative or palliative surgery, the objective of which is to eliminate microscopic debris (arthroscopic lavage, debridement),
- repair surgery, the objective of which is to form fibrocartilage by stimulating stem cells from the subchondral bone marrow (drilling of the subchondral bone, abrasion, implantation of membrane or matrix (AMIC), microfractures),
- replacement of the damaged part of the joint (unicompartmental knee prosthesis),
- restorative surgery, the objective of which is to reconstruct the microarchitecture of the cartilage to restore its biomechanical and physiological functions (mosaicplasty, osteochondral allograft, chondrocyte autograft or autologous chondrocyte or stem cell implantation).

None of the current surgical techniques has demonstrated its superiority by comparison with the others.

Similarly, the benefit of surgical techniques by comparison with drug treatment combined with rehabilitation is not known.

The place of autologous chondrocyte implantation

The SPC for CHONDROCELECT states that an autologous chondrocyte graft (autologous chondrocyte implantation, ACI) must be considered only for traumatic lesions.

Several surgical techniques can also be offered, depending on the nature, size and depth of the lesion and the patient’s expectations:
- if the subchondral bone is affected: microfractures if lesions < 2 cm\textsuperscript{2}; mosaicplasty autograft for lesions of 2-4 cm\textsuperscript{2}; chondrocyte autograft if lesions > 4 cm\textsuperscript{2}.
- if a weight-bearing area of at least 2 cm\textsuperscript{2} is affected: mosaicplasty autograft or chondrocyte grafts if there is major substance loss (> 4 cm\textsuperscript{2}).

According to the group of experts consulted by HAS in 2005, the indications for ACI are:
- “patient aged 15 to 45-50 years taking account of the level of physical activity
- with symptomatic, unipolar traumatic loss of chondral substance (subjective IKDC or ICRS score < 55), preferentially of the femoral condyle;
- after non-surgical treatment;
- and according to the size of the lesion
  - between 1 and 3 cm\textsuperscript{2}: microfractures, osteochondral autograft, or autologous chondrocyte implantation,

\textsuperscript{21} grade III “severely abnormal”: lesions of more than 50% thickness which may reach the subchondral bone. A distinction is made between lesions which leave the calcified layer intact (grade IIIa) or cross it (grade IIib), those affecting the subchondral layer (grade IIIc) and those rated as deep and destructive (grade IIIId);
- grade IV: osteochondral lesions (affecting the subchondral bone, affecting the superficial layer and impairing the bone surface).

- between 3 and 8 cm²: osteochondral autograft or autologous chondrocyte implantation,
- above 8 cm², autologous chondrocyte implantation is not recommended.

- and a correct or corrected mechanical environment (ligaments, meniscus, limb alignment).
- in cases of osteochondritis with non-recoverable substance loss (detached mobile fragment), offer osteochondral or chondrocytic autograft”.

According to the experts consulted at that time, ACI is contraindicated in patients with inflammatory and synovial diseases, osteoarthritis, mirror lesions, lesions ≤ 1 cm² and total meniscectomy. Excess weight, smoking and expected poor compliance with rehabilitation are regarded as relative contraindications. In the absence of available clinical data, uncertainties remain as regards pregnant women and patients under 18 years of age.

In cases of osteochondritis with non-recoverable substance loss (detached mobile fragment), osteochondral or chondrocytic autograft is recommended by these experts.

An appropriate rehabilitation programme to avoid early damage that could lead to graft failure after implantation must be undertaken. Excessively early and intense activity can indeed jeopardise the graft.

Place of ACI with CHONDROCELECT (with or without periosteal flap)

In view of:
- the lack of efficacy demonstrated using clinical criteria,
- the frequency of adverse effects, which is greater than with the microfracture technique which, although they are not serious in nature, are more common and may possibly jeopardise the benefit of this major surgery and have a potentially negative impact on patients’ rehabilitation,
- the need for two hospitalisations, one for arthroscopy to harvest the chondrocytes, the other for arthroscopy for their implantation and their maintenance by means of a periosteal flap, the suture for which on the periphery of the cartilage is tricky and may not last,

the place of CHONDROCELECT in therapeutic use cannot be established.

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In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

"Cartilage lesions are difficult to diagnose clinically since there is no correlation between clinical symptoms and the condition of the cartilage. Since the cartilage has no innervation, there is no sensitivity to early lesions. The symptoms vary with pain, swelling and impaired mobility possibly associated with a major impact on the quality of life." (HAS, 2005).

Deep, symptomatic lesions in a weight-bearing area can cause pain in the knee and loss of joint function leading to disability and marked impairment of the quality of life. Cartilage lesions can progress to osteoarthritis, a chronic degenerative joint disease which can be serious and disabling.

Spontaneous scar formation in these lesions is difficult if not impossible, since the capacity of joint cartilage to repair itself is very limited. The consensus view is that surgical treatment is possible only for symptomatic knee cartilage lesions of grade III and IV in the arthroscopic classification.

CHONDROCELECT is a curative treatment which may prevent the occurrence of osteoarthritis in cases where it is effective in the early repair of cartilage lesions.

In view of:
- the lack of efficacy demonstrated using clinical criteria,
- observed adverse effects which, although not serious, are very common (47.1% arthralgia, 27.4% cartilage hypertrophy, 17.6% joint crepitation 13.7% joint swelling), are more common than with the microfracture technique, and may potentially jeopardise the benefit of this major surgery and have a potentially adverse effect on patients' rehabilitation,
- the technical complexity which necessitates two hospitalisations, one for arthroscopy to harvest the chondrocytes, the other for arthrotomy for their implantation and their maintenance by means of a periosteal flap, the suture for which on the periphery of the cartilage is tricky and may not last,

the efficacy/adverse effects ratio for CHONDROCELECT has not been clearly established.

Surgical alternatives are available. Apart from palliative treatments for the elimination of microscopic debris (arthroscopic lavage and debridement), there are several possible treatments: osteochondral stimulation techniques leading to the appearance of fibrocartilage (microfractures, perforation of the subchondral bone after Pridie, abrasion) in patients with fairly small lesions; techniques for cartilage repair by replacement: osteochondral allografts and autologous osteocartilaginous grafts (mosaicplasty) as alternatives to autologous chondrocyte implantation. Analgesic treatment combined with rehabilitation may be necessary.

Public health benefit:

Little is known about the prevalence and incidence of osteochondral loss. It has multiple origins and the commonest cause in young subjects is a sports injury. It can lead to impaired quality of life and ultimately progress to osteoarthritis, particularly with injuries in weight-bearing areas, without that progression being properly documented. The public health burden of these conditions may therefore be rated as small for the subpopulation of patients likely to benefit from autologous chondrocyte implantation, i.e. adult patients with localised and symptomatic grade III and IV lesions.

The prevention of osteoarthritis, to which CHONDROCELECT could contribute, may be a public health need that is an established priority, by helping to reduce the functional impairment and incapacity induced by osteoarthritis and to improve the quality of life of the persons affected (Public Health Law 2004, Plan to improve the quality of life of patients with chronic
diseases). However, in the absence of information about the long-term prevention of osteoarthritis, CHONDROCELECT is unlikely to provide an additional response to the identified public health need.

In view of the data available on a limited number of patients, the impact of treatment with CHONDROCELECT on functional impairment and quality of life cannot be established, despite obtaining hyaline cartilage histologically.

In addition, an increase in adverse effects by comparison with the microfracture technique and short-term complications linked to the implant have been found.

The transferability of results from the pivotal study to current practice is not guaranteed (exclusion criteria particularly in patients with other articular complaints, need for patient compliance with the rehabilitation programme).

In addition, carrying out implantation involves at least two hospitalisations (performance of arthroscopy and biopsies in one, then implantation of the cells during arthrotomy in the other) whereas the microfracture technique requires just one hospitalisation. CHONDROCELECT can therefore be expected to have a potentially negative impact on the healthcare system.

Consequently, taking account of this information, CHONDROCELECT is not expected to have any public health benefit.

In view of this information, although the Committee believes that this is an innovative biotechnology, the Committee believes, on the basis of its assessment criteria, that the actual benefit of CHONDROCELECT is insufficient to justify its reimbursement by National Health Insurance in the indication of the Marketing Authorisation.

The Transparency Committee does not recommend inclusion on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

011.2 Improvement in actual benefit (IAB)

Not applicable

011.3 Target population

Not applicable
## Appendix 1: RMP

<table>
<thead>
<tr>
<th>Event</th>
<th>Proposed pharmacovigilance action</th>
<th>Proposed risk minimisation action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential major risk</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Partial or complete delamination of the periosteal flap, synovitis, damage to the subchondral bone | • Routine pharmacovigilance  
• Proactive training programme for orthopaedic surgeons and their teams in use of the product and the associated procedures.  
• Request reports on adverse events and interaction with the surgeon on the basis of the patient’s medical record.  
• Medical information and feedback to the surgeon. | • Information in section 5.3 of the SPC on the discovery of synovitis and impairment of the subchondral bone.  
• Proactive training programme as part of a controlled distribution system. |
| **Identified major risk**                                            |                                                                                                                                                      |                                                                                                                                                        |
| Symptomatic hypertrophy of the cartilage, swelling of the knee joint, knee joint crepitation, effusion of liquid in the joint, arthrofibrosis, inefficacy of the treatment (treatment failure) | • Routine pharmacovigilance  
• Proactive training programme for orthopaedic surgeons and their teams in use of the product and the associated procedures.  
• Request reports on adverse events and interaction with the surgeon on the basis of the patient’s medical record.  
• Medical information and feedback to the surgeon. | • Information in section 4.8 of the SPC on the incidence of events.  
• Information in section 4.8 of the SPC specifying that the occurrence of cartilage hypertrophy may be associated with use of a periosteal flap instead of a biological membrane.  
• Information in section 4.4 of the SPC on the risk of arthrofibrosis or inefficacy in patients with a concomitant disease of the knee or on the administration of CHONDROCELECT in patients for whom it is not indicated.  
• Proactive training programme as part of a controlled distribution system. |
| **Important missing information**                                    |                                                                                                                                                      |                                                                                                                                                        |
| Long-term durability of the repair; clinical data in patients with larger lesions (> 4 cm²); confirmation of the clinical data in patients with smaller lesions | • Routine pharmacovigilance  
• Proactive training programme for orthopaedic surgeons and their teams in use of the product and the associated procedures.  
• Request reports on adverse events and interaction with the surgeon on the basis of the patient’s medical record.  
• Medical information and feedback to the surgeon. | • Additional post-marketing data on safety and efficacy. |

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