HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

NATIONAL COMMITTEE FOR THE EVALUATION OF MEDICAL DEVICES AND HEALTH TECHNOLOGIES (CNEDiMTS)

OPINION

21 December 2010

CONCLUSIONS	
Name:	**CHONDRO-GIDE**, collagen membrane
Models and references:	Those proposed by the applicant (cf. page 2)
Manufacturer:	**GEISTLICH PHARMA AG (Switzerland)**
Applicant:	**GEISTLICH PHARMA France**
Claimed indications:	Coverage of traumatic chondral or osteochondral defects classified as grade 3 or 4 according to the International Cartilage Repair Society (ICRS) and treated by autologous chondrocyte implantation.
Available data:	Seven published clinical studies have been supplied: 2 randomised studies, 4 prospective non-comparative studies and one retrospective study. - One single-centre controlled, randomised study compared mosaicplasty with autologous chondrocyte implantation (n=100). Of the patients who underwent autologous chondrocyte implantation, 46 received a CHONDRO-GIDE membrane and 6 a periosteal cover. The follow-up period was 12 months - One single-centre randomised study compared two methods of autologous chondrocyte implantation, one using periosteal flap and one using CHONDRO-GIDE (n=68). The follow-up period was 24 months - Four prospective, non-comparative studies reported the clinical and arthroscopic results of autologous chondrocyte implantation using CHONDRO-GIDE (n=14, 30, 63 and 59). The follow-up periods were 33, 12, 36 and 24 months respectively. No retrospective study was accepted.
Actual Benefit (AB):	**Insufficient** The therapeutic benefit of the product cannot be established in autologous chondrocyte implantation because of the methodological limitations of the available studies and the difficulty of interpreting their results. The CHONDRO-GIDE membrane cannot be considered as an innovative technology on its own. The Committee nevertheless recognised the innovative nature of autologous implantation overall, including the medical procedure, a membrane or three-dimensional matrix and the suspension of autologous chondrocytes.

Taking into consideration the innovative and evolving nature of autologous chondrocyte implantation overall, the HAS Board proposes implementation of Article L.165-1-1 of the French Social Security Code.

Definitive opinion 1

EVIDENCE REVIEW

Nature of the application

Application for inclusion on the list of products and services qualifying for reimbursement mentioned under article L. 165-1 of the French Social Security Code.

- **Models and references**

CHONDRO-GIDE is available in three sizes:

- 20 x 30 mm
- 30 x 40 mm
- 40 x 50 mm

- **Packaging**

Unitary packaging.

- **Applications**

The application relates to the following indications:
Coverage of traumatic chondral or osteochondral defects classified as grade 3 or 4 according to the International Cartilage Repair Society (ICRS) and treated by autologous chondrocyte implantation.

Reimbursement history

This is the second application for inclusion on the LPPR list (List of Reimbursable Products and Services).
Because CHONDRO-GIDE can be used with chondrocytes obtained using specific cell culture techniques, this application for inclusion on the LPPR list was submitted in parallel with the application for inclusion of the autologous cell therapy product, CHONDROCELECT, on the list of medicinal products approved for hospital use. The Transparency Committee opinion of 6 October 2010 (made official on 26 October 2010) on its inclusion on the list of medicinal products approved for hospital use was unfavourable.

The first request for inclusion of CHONDRO-GIDE on the LPPR list, in 2006, concerned 2 indications: the treatment of traumatic cartilage defects, located in the femoral condyle (lateral, medial, trochlear) and in the patella, when the method of treatment is autologous matrix-induced chondrogenesis (AMIC) or autologous chondrocyte implantation (ACI).
On 24 January 2007, the Committee issued an unfavourable opinion owing to:
- the lack of authorisation to perform autologous chondrocyte implantation routinely in France. The Committee considered it was premature to approve CHONDRO-GIDE, associated with this technique, for inclusion on the list of products and services provided for under Article L165.1 of the French Social Security Code
- the lack of sufficient clinical data showing the benefit of CHONDRO-GIDE in AMIC.

Characteristics of the product and the associated service

- **CE marking**

Class III, notification by TÜV Product Service (no. 0123), Germany.

- **Description**

The CHONDRO-GIDE collagen membrane of porcine origin is a bilayer matrix with a compact smooth surface and a porous surface. It is resorbable (within 24 weeks).

- **Intended purpose**

The CHONDRO-GIDE matrix is intended to cover traumatic cartilage defects treated by means of autologous chondrocyte implantation.
The compact layer with a smooth surface plays the role of a barrier, preventing the mesenchymal stem cells from diffusing into the joint space and protecting them against mechanical stress.
The second layer, with a porous structure, supports cell invasion and attachment.

- **Associated intervention or service**

- The procedure of harvesting chondrocytes by means of arthroscopy is already described in the French classification system for medical procedures (Classification commune des actes médicaux/CCAM) (arthroscopic knee joint exploration, NFQC001), along with irrigation of the knee joint by means of arthrotomy (NFJA001) or arthroscopy (NFJC001) and the procedure of periosteum harvesting at a distance from the site (autologous cortical or corticocancellous bone or periosteal graft harvesting at a distance from the surgical site, at a site with no change in position; PAFA010)
- The elements of the procedure which are not described in the CCAM classification system are the injection of chondrocytes beneath the periosteal cover or the placement of the collagen membrane followed by the injection of chondrocytes.
  This procedure was assessed by HAS in parallel with the assessment of the CHONDRO-GIDE device.

Actual Benefit

1. Benefit of the product or service

1.1 Data analysis: assessment of the therapeutic effect/adverse effects, risks linked to use

The supporting documentation and evidence supplied in the dossier do not assess CHONDRO-GIDE alone, but CHONDRO-GIDE as used in autologous chondrocyte implantation.
Seven published clinical studies have been supplied: 2 randomised studies[1,2] and 4 prospective, non-comparative studies[3,4,5,6]. One retrospective study was not accepted[7].

Bentley study[1] (2003)
This single-centre, controlled, randomised study compared mosaicplasty with autologous chondrocyte implantation. One hundred patients were randomised: 42 to the mosaicplasty group and 58 to the autologous chondrocyte implantation group. Of the patients who underwent autologous chondrocyte implantation, 46 received a CHONDRO-GIDE membrane, and 6 a periosteal cover. The follow-up period was 12 months.

The average defect size was 4.66 cm^2. The defects were located in the medial femoral condyle in 53 cases, the lateral femoral condyle in 18 cases, in the trochlea in 3 cases, in the patella in 25 cases and in the lateral tibial condyle in one case.
The primary endpoint was the Cincinnati functional assessment score (out of 100), modified by the authors as follows: Excellent: > 80; Good: 55-79; Fair: 30-45; Poor: < 30.

At the last follow-up for all the patients, the results were as follows:

Modified Cincinnati score		Excellent > 80	Good 55-79	Fair 30-45	Poor < 30	p
Autologous chondrocyte implantation: n = 46 CHONDRO-GIDE n = 6 periosteum	n = 58	23	28	7	0	p = 0.277
Mosaicplasty	n = 42	9	20	6	7	

The following complications were reported, with no details regarding the treatment group with which they were associated:
- 3 cases of delayed mobilisation necessitating manipulation under anaesthesia
- 1 case of deep vein thrombosis
- 1 case of superficial infection.

[1] Bentley G, Biant LC, Carrington RWJ, Akmal M, Goldberg A, Williams AM, Skinner JA, Pringle J. A prospective, randomised comparison of autologous chondrocyte implantation *versus* mosaicplasty for osteochondral defects in the knee. J Bone Jt Surg [Br] 2003; 85-B: 223-230
[2] Gooding CR, Bartlett W, Bentley G, Skinner JA, Carrington R, Flanagan A. A prospective, randomised study comparing two techniques of autologous chondrocyte implantation for osteochondral defects in the knee: periosteum covered versus type I/III collagen covered. The knee 2006; 13: 203-210
[3] Briggs TWR, Mahroof S, David LA, Flannelly J, Pringle J, Bayliss M. Histological assessment of chondral defects after autologous chondrocyte implantation of the knee. J Bone Joint Surg [Br] 2003; 85-B: 1077-1083
[4] Haddo O, Mahroof S, Higgs D, David L, Pringle J, Bayliss M, Cannon SR, Briggs TWR. The use of chondrogide membrane in autologous chondrocyte implantation. The Knee. 2004; 11: 51-55
[5] Steinwachs M, Kreuz PC. Autologous chondrocyte implantation in chondral defects of the knee with type I/III collagen membrane: a prospective study with a 3-year follow-up. Arthroscopy 2007; 23(4): 381-387
[6] Niemeyer P, Lenz P, Kreuz PC, Salzmann GM, Südkamp NP, Schmal H, Steinwachs M. Chondrocyte-seeded type I/III collagen membrane for autologous chondrocyte transplantation: prospective 2-year results in patients with cartilage defects of the knee joint. Arthroscopy 2010; 26(8): 1074-1082
[7] Niemeyer P, Pestka JM, Kreuz PC, Erggelet C, Schmal H, Suedkamp NP, Steinwachs M. Characteristic complications after autologous chondrocyte implantation for cartilage defects of the knee joint. Am J Sports Med. 2008; 36(11): 2091-2099

Gooding study[2] (2006)

This single-centre randomised study compared two methods of autologous chondrocyte implantation, one using a periosteal cover and one using a CHONDRO-GIDE synthetic collagen membrane. Sixty-eight patients were randomised, 33 patients to the periosteum group and 35 patients to the CHONDRO-GIDE group. The follow-up period was 24 months.

The average defect size was 4.54 cm^2. The defects were located in the medial femoral condyle in 26 cases, the lateral femoral condyle in 11 cases, the trochlea in 4 cases and the patella in 27 cases.
The endpoints were:

- the Cincinnati functional assessment score (out of 100), modified as follows: Excellent: > 80; Good: 55-79; Fair: 30-45; Poor: < 30 and
- arthroscopic assessment of the defect based on the ICRS (International Cartilage Repair Society) grade.

The clinical results were as follows:

Modified Cincinnati score	**Periosteum n= 33**		**Collagen membrane n = 35**	
	Pre-surgical	After 2 years	Pre-surgical	After 2 years
Excellent > 80		10		12
Good 55-79	13	12	12	14
Fair 30-45	11	7	17	5
Poor < 30	9	4	11	4
p	p < 0.005		p < 0.005	

The arthroscopic results are reported below:

ICRS grade	**After 1 year**		**After 2 years**	
	Periosteum	Collagen membrane	Periosteum	Collagen membrane
Excellent	3	3	-	1
Good	22	20	5	8
Fair	5	5	3	2
Poor	1	1	1	
Total	31	29	9	11
	NS		NS	

The authors reported the following complications:
- 3 major complications after 1 year:
1 case of deep vein thrombosis in the CHONDRO-GIDE group and 2 cases of graft rupture in the periosteum group.

- 36 minor complications, including notably:
  - 14 cases of cartilage hypertrophy:
    - 1 case after 2 years in the CHONDRO-GIDE group and
    - 12 cases after 1 year and 1 case after 2 years in the periosteum group
  - One case of superficial infection in the periosteum group.

Methodological limitations of these two randomised studies

In the absence, notably, of an *a priori* calculation of the number of subjects required, any details regarding the randomisation procedures and any information on group comparability, the results of these studies cannot be interpreted.

Prospective studies

Four prospective, non-comparative studies reported the clinical and arthroscopic results of autologous chondrocyte implantation with use of CHONDRO-GIDE (n=14, 30, 63 and 59). The follow-up periods were 33, 12, 36 and 24 months respectively.

The assessment criteria were

- various algofunctional knee assessment criteria (Brittberg score, Tegner Lysholm knee scoring scale, Lysholm-Gillquist score, Meyers score, Cincinnati functional assessment score and International Knee Documentation Committee (IKDC) score)
- a pain score (verbal numeric pain scale) and
- an arthroscopic defect assessment criterion (ICRS (International Cartilage Repair Society) grade)

The table below summarises the characteristics of these 4 prospective non-comparative studies.

Table 1. Characteristics of prospective non-comparative studies – Autologous chondrocyte implantation with use of CHONDRO-GIDE

Authors	Follow-up	Patients	Defect characteristics	Endpoints
Briggs[3] (2003)	33 months	n=14	Not specified	Algofunctional knee assessment: - Brittberg score (excellent / good / fair / poor) - Tegner-Lysholm score (0-100) - Lysholm-Gillquist score (0-100) Verbal numeric pain scale
Haddo[4] (2003)	12 months	n=30	Average size: 2.86 cm^2 Anatomical site: - medial femoral condyle: 20 - lateral femoral condyle: 7 - trochlea: 2 - patella: 4	Algofunctional knee assessment: - Brittberg score (excellent / good / fair / poor) - Meyers score (0-20) - Lysholm-Gillquist score (0-100) Verbal numeric pain scale
Steinwachs[5] (2007)	36 months	n=63	Average size: 5.85 cm^2 Anatomical site: - femoral condyles: 34 - trochlea: 10 - patella: 19	Cincinnati functional assessment score (0-100) Objective knee examination: ICRS grade
Niemeyer[6] (2010)	24 months	n=59	Average size: 4.64 cm^2 Anatomical site: - medial femoral condyle: 15 - lateral femoral condyle: 8 - trochlea: 3 - patella: 14 - multiple: 19	Objective knee examination: ICRS grade Algofunctional knee assessment: - IKDC (International Knee Documentation Committee) score - Lysholm-Gillquist score (0-100) - Tegner-Lysholm score (0-100)

The results of these 4 prospective, non-comparative studies tend to show an improvement in the endpoints post-operatively compared with the assessed pre-surgical status.

Because of their design, however, these studies do not enable conclusions to be drawn regarding the contribution made by CHONDRO-GIDE in autologous chondrocyte implantation.

1.2 Therapeutic use

The surgical therapeutic alternatives to the treatment of losses of chondral substance from the knee are described in the Haute Autorité de Santé progress report on the assessment of autologous chondrocyte implantation for the knee[8].

The existing surgical techniques for treating cartilage defects include conservative or palliative surgery, reparative surgery, restorative surgery and prosthetic surgery.

Type of surgery	**Objective**	**Interventions**	**State of assessment of the technique / Management**	**Therapeutic use**
Conservative or palliative	Elimination of microscopic debris	- Arthroscopic irrigation - Debridement	CCAM procedure CCAM procedure	
Reparative	Fibrocartilage formation by stimulation of stem cells from the subchondral bone marrow	- Drilling of the subchondral bone - Abrasion - Microfractures (princeps technique) - Microfractures + membrane or matrix = AMIC (2nd method claimed in CHONDRO-GIDE application for inclusion in 2006)	CCAM procedure Procedures not identified in the CCAM	First-line
Restorative	Reconstruction of the cartilage microarchitecture to restore its biomechanical and physiological functions	- Mosaic-like implantation of multiple autologous osteochondral implants: mosaicplasty - Osteochondral allograft - **Autologous chondrocyte implantation**	Procedures assessed by the HAS in May 06 Procedures not identified in the CCAM	Second-line
Prosthetic	Replacement of the damaged part of the joint	Unicompartmental knee prosthesis	- CCAM procedure - Implants included on the LPPR list	After failure of previous alternatives (+ 60 years of age)

According to the 2005 HAS report, *the surgical technique of autologous chondrocyte implantation using a periosteal cover is evolving towards the use of matrix or membrane. The techniques using matrices have either been assessed or are in the process of being assessed. Matrices are thought to offer technical advantages: no periosteum harvesting and suture, possibility of implantation using arthroscopy and a biological advantage through better spatial distribution of chondrocytes. The research with stem cell use is currently at an experimental stage.*

A few clinical trials of autologous chondrocyte implantation with *periosteal cover*, membrane or three-dimensional matrix use are in progress at present.
At the present time, no cell therapy unit is authorised to perform autologous chondrocyte preparation routinely in France.

ChondroCelect® is the only cell therapy product to have obtained a Marketing Authorisation in Europe (October 2009).

[8] Haute Autorité de Santé. Assessment of autologous chondrocyte implantation for the knee – Progress report, February 2005. www.has-sante.fr

On 6 October 2010, the Transparency Committee issued an unfavourable opinion in respect of its inclusion on the list of medicinal products approved for hospital use.
The Transparency Committee's conclusion was as follows: "Although the Committee considers ChondroCelect® to be an innovative biotechnology, the medical benefit it provides must be considered provisionally as insufficient, on the basis of the data as they stand at present, to justify its reimbursement.
The Committee is not in a position to assess its therapeutic benefit, particularly with regard to the long-term prevention of osteoarthritis".

In addition to the 2005 HAS report, three more recent international assessment reports have also been identified: the National Health Service report (United Kingdom, 2005)[9], the Spanish Ministry of Health report (2007)[10] and the Ludwig Boltzmann Institute report (Austria, 2009)[11]. These assessment reports are consistent in stating that there is insufficient evidence to affirm that autologous chondrocyte implantation is more effective than other techniques, with non-inferiority of autologous chondrocyte implantation having been demonstrated in the short-term, and no long-term data being available.
Moreover, taking into account the cost of this technique, the assessment reports all conclude that there is a need to assess its cost-benefit ratio in properly conducted studies.

In view of these different assessments, the therapeutic use of autologous chondrocyte implantation cannot be defined.

Furthermore, the specific therapeutic benefit of CHONDRO-GIDE is not established in autologous chondrocyte implantation because of the methodological limitations of the studies available and the difficulty of interpreting their results.

2. Expected public health benefit

2.1 Seriousness of the condition

When cartilage is damaged, it has limited capacity for repair, and the defects are usually irreversible. High-grade chondral losses can be replaced naturally with fibrocartilaginous tissue derived from bone marrow stem cells, but this neotissue is non-functional.

Cartilage defects are likely to develop into osteoarthritis, particularly when the defects are located in weight-bearing regions.

Chondral and osteochondral defects are the source of a deterioration in quality of life; their development into osteoarthritis is liable to result in disability.

2.2 Epidemiology of the condition

The prevalence and incidence of chondral loss are not known. Cartilage defects which may be candidates for chondrocyte implantation are those which occur in patients with dissecting osteochondritis or which are secondary to knee instability caused by a ligament lesion or by a meniscal problem. In the young subject, the most frequent cause is sports injury.

No specific French epidemiological data have been published.

[9] Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, et al. Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic assessment. Health Technol Assess 2005; 9(47)
[10] Pérez Cachafeiro S, Ruano Raviña A, Grupo de trabajo del trasplante autólogo de condrocitos. Implante autólogo de condrocitos: revisión sistemática y ampliación del seguimiento del uso tutelado. Madrid: Ministerio de Sanidad y Consumo. Avalia-t Nº 2006/05
[11] Künzl M, Mathis S, Johansson T, Wild C. Autologous chondrocyte implantation – Systematic Review. HTA ProjektBericht. 2009; 34

In a prospective American series[12] of 1,000 consecutive arthroscopies, 606 of them (61%) showed chondral or osteochondral defects. Chondral or osteochondral loss was identified in 193 arthroscopies (19%), with single defects in 80% of the cases. Single defects classified as ICRS grade 3 or 4, measuring a minimum of 1 cm^2, were found in 5.3% of the patients aged below 40, in 6.1% of those under 45 years of age and in 7.1% of patients under the age of 50.
According to 2 assessment reports, the prevalence of chondral lesions revealed by arthroscopy in subjects under 40 years of age was estimated at 4%[13] in one, and 5%[14] in the other.

According to the Haute Autorité de Santé progress report assessing autologous chondrocyte implantation for the knee[2], 5% of the arthroscopies performed each year in France identify isolated, high-grade (stage III and IV) chondral loss in weight-bearing condyle areas.

2.3 Impact

CHONDRO-GIDE meets a therapeutic need which is covered (cf. § 1.2).

The treatment of cartilage defects by means of autologous chondrocyte implantation is of public health benefit in view of the serious nature of this condition.

In conclusion, the National Committee for the Evaluation of Medical Devices and Health Technologies (Commission Nationale d'Evaluation des Dispositifs Médicaux et des Technologies de Santé/CNEDiMTS) considers that the Actual Benefit of CHONDRO-GIDE is insufficient for it to be included on the list of products and services mentioned under article L. 165-1 of the French Social Security Code.

The CHONDRO-GIDE membrane cannot be considered as an innovative technology on its own. The Committee nevertheless recognised the innovative nature of autologous implantation overall, including the medical procedure, a membrane or three-dimensional matrix and the suspension of autologous chondrocytes.

[12] Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. Arthroscopy 2002; 18(7): 730-734
[13] Swedish Council on Technology Assessment in Health Care. Autologous chondrocyte transplantation in treating cartilage damage in the knee. SBU Alert 1999; 15(Version 1)
[14] Jobanputra P, Parry D, Fry-Smith A, Burls A. Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review. Health Technol Assess 2001; 5(11)