TECHNICAL DOSSIER

DiscoGel®
(ethanol, derivative of cellulose, tungsten)

MEDICAL DEVICE

CLASS D

VERSION 07/06/2013
1. Executive summary

This file has been prepared to fulfill any requirement demanded by the Ministry of Health and Medical Education of the Islamic Republic of Iran.

Our product here described hereafter, corresponds to a medical device class D: Implant.

In addition to the table of contents, which corresponds to the information requested by the application form for a medical device registration, Gelscom added some annexes.

These annexes are composed of:

- Artworks: labels and packaging of the device (kit)
- The last version of the notice – Instruction of use
- Quality Management certificate (ISO 13485)
- Last updated CE approval certificates
2. Table of contents

1. Executive summary ................................................................................................................................................ 2
2. Table of contents .................................................................................................................................................... 3
3. Device Description .................................................................................................................................................. 4
4. Design Philosophy .................................................................................................................................................. 4
   4.1 Research orientation ......................................................................................................................................... 4
   4.2 International patent .......................................................................................................................................... 4
   4.3 Description of the mechanism of action .......................................................................................................... 4
   4.4 Final design of DISCOGEL ............................................................................................................................ 5
5. Marketing History ................................................................................................................................................... 6
6. List of Standards ..................................................................................................................................................... 7
7. Method of Sterilization ........................................................................................................................................... 8
   7.1 Referential applied ......................................................................................................................................... 8
   7.2 Process description ....................................................................................................................................... 8
8. Summary of Safety and Effectiveness Studies of DISCOGEL® ........................................................................... 8
   8.1 Retrospective study on 337 cases during 4 years .......................................................................................... 8
   8.2 Retrospective study presentation (initial clinical data) ............................................................................... 9
   8.3 Additional initial study on cervical discs ...................................................................................................... 11
   8.4 Animal study (Pig) ........................................................................................................................................ 11
   8.5 Post market studies .................................................................................................................................... 11
   8.5.1 Observational open prospective study on 79 patients ............................................................................. 11
   8.5.2 Observational open prospective study on 35 patients (Pending publications) ........................................ 12
9. Risk management Report .................................................................................................................................... 13
   9.1 Logigram of analysis ................................................................................................................................. 13
   9.2 Rules of quantification: ............................................................................................................................ 14
   9.3 Medical device vigilance records on the 07/06/2013 ............................................................................... 17
   9.4 Conclusion of risks analysis: .................................................................................................................... 17
10. Material Specifications ....................................................................................................................................... 17
11. Annexes ............................................................................................................................................................. 18
   Annex 1: labeling material ............................................................................................................................ 19
   Annex 2: Instruction for use (recto & verso) .................................................................................................. 21
   Annex 3: Quality management certificate ....................................................................................................... 23
   Annex 4: CE approval .................................................................................................................................... 24
3. Device Description

As indicated in the “instruction for use”, DISCOGEL® comes in the form of a kit ready for the use with the following characteristics:

- One type I glass bottle containing 2.2mL of solution for injection composed of a mixture ethyl alcohol, cellulose derivative product and radio opaque agent (tungsten),
- Two 1mL syringes,
- One high-flow 19G5 needle,
- Two 18G spinal injection needles,
- One descriptive notice.

4. Design Philosophy

4.1 Research orientation

The initial idea comes from the practice of percutaneous injections of Chymopapain* or Ethanol (nucleolysis)**
Compensate disadvantages of these products and keep the minimally procedure
Limit the spreading of ethanol in healthy tissues and play on its hydrophilic power
Find a “compatible sponge” with ethanol to avoid leakage
Find a contrast compound enabling to trace the injection in the disc.

4.2 International patent

One International patent registered under the number WO 03/097108A1 was submitted and registered.

* CEDIT ref. 57: Percutaneus nucleolysis with Chymopapain: gold standard in France 1980-1990
** Riquelme C, Musacchio M, Mont’Alverne F, Tournade A, Chemonucleolysis of lumbar disc herniation with ethanol.
   J Neuroradiol 2001, 28 ; 219-229

4.3 Description of the mechanism of action

This ethanol gel induces a Liquid migration from the disc hernia toward the center of the disc, resulting in the disc decompression.
The ethanol has a hydrophilic effect, supporting the liquid migration
In contact with water, the cellulose derivative component of the gel flocculates in the micro-infractions of the disc, leading to a self-print, consolidation and filling of the weakened parts of the disc, as a “protection barrier”.
This barrier stops inflammatory compounds *** out of the disc at the origin of the pain.

*** collagens inside the disc are very immunogenic.
Please have a look on the following schematic drawing to illustrate the mechanism of action claimed and expected:

4.4 Final design of DISCOGEL

The commercial design of the product should respect the following criteria:

- Easy to use (because designed by users and practitioners at the very beginning)
- Efficient to resorb the herniated disc (at any level of spine)
- Limit the risk of leakage of the gel out of the disc
- Behave as a soft prosthesis (respecting as much as possible spine mechanical properties)
- Enable a follow up during the procedure (trace on fluoroscope)
- Combined to a minimally invasive technique
- A day hospital treatment
- Avoid problem with incompatible injection elements to undergo the procedure
- Make some substantial pharmaco economic savings (limit post treatment complications, sequel)
5. Marketing History

Please find here after a list of countries where GELSCOM has supplied DISCOGEL®.

* Territories recently initiated.

<table>
<thead>
<tr>
<th>Areas in Europe</th>
<th>Areas outside Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albanie*</td>
<td>Asia:</td>
</tr>
<tr>
<td>Andora</td>
<td>Hong-Kong *</td>
</tr>
<tr>
<td>Austria</td>
<td>Maghreb:</td>
</tr>
<tr>
<td>Bosnia Hertzegovina</td>
<td>Tunisia</td>
</tr>
<tr>
<td>Croatia*</td>
<td>Meadle East:</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Bahreim</td>
</tr>
<tr>
<td>France</td>
<td>Egypt</td>
</tr>
<tr>
<td>Germany</td>
<td>Lebanon</td>
</tr>
<tr>
<td>Greece</td>
<td>Qatar</td>
</tr>
<tr>
<td>Italy</td>
<td>Unated Arab Emirate</td>
</tr>
<tr>
<td>Kosovo*</td>
<td>Latin America:</td>
</tr>
<tr>
<td>Montenegro*</td>
<td>Argentina</td>
</tr>
<tr>
<td>Portugal</td>
<td>Chili</td>
</tr>
<tr>
<td>Romania</td>
<td>Mexico*</td>
</tr>
<tr>
<td>Slovenia</td>
<td>Peru</td>
</tr>
<tr>
<td>Serbia*</td>
<td>Africa:</td>
</tr>
<tr>
<td>Spain</td>
<td>West African Area (Senegal,...)</td>
</tr>
<tr>
<td>Switzerland</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td></td>
</tr>
</tbody>
</table>

GELSCOM is dealing in more than 20 countries to get new registration of its products together with local exclusive distributors at the moment.

Up to now, we also inform there have not been any Health or Sanitary warnings or alerts related to the use of the products or the products themselves or received a demand/claim against any of the products sold, in any of the countries listed above.
6. List of Standards

The declaration of conformity here after describes the EN ISO standard applied for DISCOGEL®.
7. Method of Sterilization

DISCOGEL® is a medical device class D (implant) the ethanol gel inside each vial must comply with the normative international essential requirements for steam sterilization.

7.1. Referential applied

<table>
<thead>
<tr>
<th>Referential</th>
<th>Associated text</th>
</tr>
</thead>
<tbody>
<tr>
<td>EN ISO 556-1:2001</td>
<td>Sterilization of medical devices - Requirements for medical devices to be designated &quot;STERILE&quot; - Part 1: Requirements for terminally sterilized medical devices</td>
</tr>
<tr>
<td>EN ISO 17665-1:2006</td>
<td>Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices</td>
</tr>
<tr>
<td>EN ISO 11737-1:2006</td>
<td>Sterilization of medical devices - Microbiological methods - Part 1: Determination of a population of microorganisms on products</td>
</tr>
</tbody>
</table>

7.2. Process description

GELS COM has decided to perform:

- A biodurden of the radio opaque ethanol gel before any sterilization cycle
- An endotoxin research in the finalized product
- Periodic use of Bacterial Indicators test (thermo resistant bacteria elimination during a sterilizing cycle)

The process is periodically reviewed as requested by the normative instructions.

8. Summary of Safety and Effectiveness Studies of DISCOGEL®

8.1 Retrospective study on 337 cases during 4 years

The retrospective collection and the analysis of clinical data of DISCOGEL® showed, on an important series of 337 patients over 4 years, the remarkable effectiveness of the product. This effectiveness is comparable to that of another treatment, the chymopapaine [1], who was managed for a long time by percutaneous injection in the same indications. However, chymopapaine introduced rare though incontestable allergic complications. It was unadvised to use it a second time on the same patient. It was been finally withdrawn from the market in 2002 for reasons linking allergic risk to purely commercial decisions.

In the opposite, clinical data highlight a very good tolerance of DISCOGEL®, without toxicity linked to the act or to the product. Moreover, these same data did not highlight risk or particular pressure of the surgical very act, this one calling a classical gesture in interventional neuroradiology.

One of the alternative treatments in the chymopapaine [1] is ethanol injection in the intravertebral disc [3], [4]. The capacities of drainage of the ethanol allow the resumption of hernia. On the other hand, it is impossible to control nor the precise site of injection (the ethanol is not opaque in X-rays), nor to avoid its migration in ambient cloths. The conception of DISCOGEL® is intended for landing these two disadvantages [5], [6], [7].
• The presence of a radio-opaque compound allows to show the fissures of the disc (confirming forecast so), the progression of the product in the course of injection and as part of the post surgical monitoring of the patients;
• The macromolecule (derivative of cellulose) in its three dimensional network sequestrates the ethanol. This jellification limits ethanol migration in neighbour tissues. This sequestration in situ reinforces the duration ethanol action.
• The deposition of the tungsten mixed with (derivative of cellulose) reinforces the weak parts of the disc and makes one implant.
• This implant might also explain the limitation of pro-inflammatory molecules that irritate the surrounding spinal roots of the herniated disc.

The described population is representative of the population of patients requiring this type of intervention. This is true for demographic criteria as for the locations of the treated discs, antecedents and the linked treatments.

The offered doses, indications discreet and demanded of location and the possible association in local acts (nucleotomy, corticoids in posterior intra-articular injection) make of DISCOGEL® an ideal candidate for the treatment of this disease by nucleolysis.

Finally this day, after more than a year after the fence of this study, the installation of the consecutive medical device vigilance in the use of DISCOGEL® does not contradict the current valuation of the product.

8.2 Retrospective study presentation (initial clinical data)

« Percutaneous treatment of lumbar intervertebral disk hernias with radiopaque gelified ethanol – A preliminary study” - Journal of Spinal Disorders and Techniques. 20(7):526-532, October 07

• Population :

276 patients (160 men and 116 women), from 19 to 83 years, candidates for a percutaneous treatment for a lumbar herniated disc.
Symptomatology: Lumbago + Radicular pain (195), the only Lumbago (54), Radicular pain only (19), hyperalgic Hernia (8).
### Methodology and results:

<table>
<thead>
<tr>
<th>Groups of treatment</th>
<th>Group A 221 patients</th>
<th>Group B 44 patients</th>
<th>Group C 11 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of treatment</td>
<td>Narrow channel (41), Hernia foraminal (6) Hernia hyperalgic without sleep (8)</td>
<td>1 level only (maj. L4/L5)</td>
<td></td>
</tr>
<tr>
<td>Kind of treatment</td>
<td>DISCOGEL + Intra-articular Steroid AI</td>
<td>DISCOGEL + automated percutaneous nucleotomy + Intra-articular Steroid AI</td>
<td>DISCOGEL + nucleoplasty by radiofrequency + intra-articular Steroid AI</td>
</tr>
<tr>
<td>Procedure (local anaesthesia, in right lateral decubitus, under digital fluoroscopy)</td>
<td>Injection: 0.4 to 0.8 ml of DISCOGEL + 1 - 3 mg of gentamicine + 20 mg of triamcinolone acetonide (at least 1 facet pronunciation)</td>
<td>Post-injection: Anti inflammatories and sedative analgesic up to monitoring consultation (15 days).</td>
<td></td>
</tr>
<tr>
<td>Results*</td>
<td>Very good and good: 91.4%</td>
<td>Very good and good: 84%</td>
<td>Very good and good: 82%</td>
</tr>
<tr>
<td>1 – Pain</td>
<td>Very good: absence of pain - no limitation – come back to professional activity Good: intermittent pain - trifling limitations - come back to professional activity</td>
<td>Reduction marked with the volume of hernia</td>
<td></td>
</tr>
<tr>
<td>2 - Hernia</td>
<td>Any radicular pain burn sensation during or after procedure Light lack of comfort at the level of the disc at the beginning of injection, disappearing in the course of injection No allergic reaction, no infection No pathology of late appearance linked up with injection (followed of 4 years for the first patients).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8.3 Additional initial study on cervical discs

“Percutaneous treatment of cervical disk hernias using gelified ethanol”

**Summary:** This study investigates the efficacy of chemonucleolysis using RGE in the treatment of cervical disk hernias in a small sample of patients who had cervical diskogenic or radicular pain secondary to disk herniation. Results were satisfactory in 89.5% patients, with no adverse events recorded during the procedure or after. The use of RGE shows promising results and might be a feasible and safe alternative in the treatment of cervical disk hernias.

8.4 Animal study (Pig)

This primary study shows that an injection in a muscle does not affect the histological structure of the muscle or nerves. This may indicate that in case of leakage of the ethanol gel outside the disc, the risk of sclerosis and damage is unlikely.

8.5 Post market studies

The initial studies performed by Pr. THERON were questionable on methodology (combination of therapies) and on indication (positive results or natural evolution?)

Other teams have performed clinical studies with DISCOGEL® alone.

8.5.1. Observational open prospective study on 79 patients

“Percutaneous treatment of sciatica caused by a herniated disc: An exploratory study on the use of gaseous discography and DISCOGEL® in 79 patients”


**Indication for enrolment:**

79 patients with lumbar radicular pain due to disc herniation resisting to (2 epidural infiltrations)

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Imagery criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 epidural infiltrations</td>
<td>Single radicular disc conflict level</td>
</tr>
<tr>
<td>Radicular AVE &gt; 50 mm</td>
<td>Disc pinch (collapse) &lt; 50%</td>
</tr>
<tr>
<td>Lasergue (Straight Leg raise) test &lt; 60°</td>
<td>Not migrated or not extruded soft herniated disc</td>
</tr>
<tr>
<td>Radicular pain &lt; 1 year</td>
<td>Absence of “Narrow lumbar level”</td>
</tr>
<tr>
<td>Accident happened at work: excluded</td>
<td></td>
</tr>
</tbody>
</table>
- **Results:**

<table>
<thead>
<tr>
<th>Duration</th>
<th>Day 0</th>
<th>Day 60</th>
<th>Day 255</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>N=79</td>
<td>N=79</td>
<td>N=64</td>
</tr>
<tr>
<td>Radicular pain</td>
<td>6.7 ±1.6</td>
<td>2.0 ±2.5*</td>
<td>2.7 ± 3*</td>
</tr>
<tr>
<td>Lumbar pain</td>
<td>6.6 ± 2.1</td>
<td>2.7 ± 2.5*</td>
<td>3.0 ± 3*</td>
</tr>
</tbody>
</table>

* Significant difference p< 0.0001 compared to day 0

<table>
<thead>
<tr>
<th>Better feeling</th>
<th>Advise to a relative</th>
<th>Back to work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient 24%</td>
<td>None 16%</td>
<td>No 22%</td>
</tr>
<tr>
<td>Sufficient 76%</td>
<td>Complete 61%</td>
<td>Yes 78%</td>
</tr>
</tbody>
</table>

- **Tolerance of DISCOGEL®:**

No disc collapse after DISCOGEL®
Few post-treatment pains: disc renitence controlled by air manometer, no DISCOGEL injection if the disc is not proof.
Recurrent pain: 3%

8.5.2. Observational open prospective study on 35 patients (Pending publications)

“DISCOGEL® in disco radicular conflicts resistant to medical treatment” - Preliminary Open study about 35 patients.

*J. Damiano, O. Tran, S. Touraine, F. Tubach, B. Hamze, V. Bousson, V. Simon, J. Beaudreuil, J-D Laredo*  
Rue du Rhumatisme 79S (2012)

- **Indication for enrolment:**

35 patients with lumbar radicular pain due to disc herniation resisting to (2 epidural infiltrations)

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Imagery criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 epidural infiltrations</td>
<td>Single radicular disc conflict level</td>
</tr>
<tr>
<td>Radicular AVE &gt; 50 mm</td>
<td>Disc pinch (collapse) &lt; 50%</td>
</tr>
<tr>
<td>Lasergue (Straight Leg raise) test &lt; 60°</td>
<td>Not migrated or not extruded soft herniated disc</td>
</tr>
<tr>
<td>Radicular pain &lt; 1 year</td>
<td>Absence of “Narrow lumbar level”</td>
</tr>
<tr>
<td>Accident happened at work: excluded</td>
<td></td>
</tr>
</tbody>
</table>
• Results: Analogic Evaluation Scale

Radicular Pain was performed by independent practitioner

<table>
<thead>
<tr>
<th>% improvement</th>
<th>After 1 month</th>
<th>After 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20%</td>
<td>65.70%</td>
<td>80%</td>
</tr>
<tr>
<td>&gt; 30%</td>
<td>57.14%</td>
<td>74.28%</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>40%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Acceptable results: Analogic Evaluation Scale < 40/100.

Score at 3 months at **68.57%**.

• Tolerance: identical in all initial studies

Delay for improvement: 4 to 6 weeks.
No allergic risk (possibility to treat again another disc)
No or small risk of collapse

• Comments:
The difference in the scores compared to Pr. J. THERON probably comes from the absence of posterior joint infiltration.
The Parisian team wants now to set up a randomized study, to confirm the previous results.

9. Risk management Report

9.1. Logigram of analysis

The identification of reasonably foreseeable danger (§4.2 and 4.3 ISO 14971:2009) is led by using as support the guide of the annex C this frame of reference.

The matrix of the definition of the acceptability of identified risks is the following:
9.2. Rules of quantification:

Risk is considered as being the combination of two elements: the likelihood of case of damage and the gravity of this damage.

The acceptability of identified risks will be function of these two criteria.

Discreet principle is semi-quantitative approach, such as the described in the annex D, §D.3.4.2 from EN ISO14971:2009.

⇒ Frequency or likelihood

Frequency or likelihood of case of damage is assessed according to a ladder at five levels defined as follows:

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - Frequent</td>
<td>Occurs practically in every use, in the life of the device (in use NC)</td>
</tr>
<tr>
<td>4 - Probable</td>
<td>Is possible occur often in the life of the device (in use NC)</td>
</tr>
<tr>
<td>3 - Occasional</td>
<td>1 time in the life of the device (in use CN) can occur at least</td>
</tr>
<tr>
<td>2 - Rare</td>
<td>1 time during the life of the device will be able (in particular conditions) to occur at least</td>
</tr>
<tr>
<td>1 - Improbable</td>
<td>Improbable in the present state of knowledge</td>
</tr>
</tbody>
</table>
Gravity

Also, the gravity of damage is assessed on a ladder at five levels defined as follows:

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - Catastrophic</td>
<td>Lesions or serious attacks possible procreate decease or deep and permanent disability</td>
</tr>
<tr>
<td>4 - Critical</td>
<td>Lesions or irreversible attacks, completely maladjusted treatment, permanent disability</td>
</tr>
<tr>
<td>3 - Important</td>
<td>Lesions or reversible attacks requiring a medical treatment, a temporary disability</td>
</tr>
<tr>
<td>2 - Feeble</td>
<td>Lesions or reversible attacks without medical treatment, feeling of faintness, discomfort</td>
</tr>
<tr>
<td>1 - Negligible</td>
<td>No lesion, no attack</td>
</tr>
</tbody>
</table>

It takes out the following matrix:

```
<table>
<thead>
<tr>
<th>Frequency</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Frequent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Occasional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Rare</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Improbable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
```

The Red zone corresponds to unacceptable risks,
The orange zone is the said zone "ALARP", where risks are considered as so weak as reasonably possible,
The green zone considered risks as allowable.
According to the frame imposed by the referential, the risk identification must undergo 34 categories of risks.

Before risk management the risks identified were considered the following:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Severity</th>
<th>Negligible</th>
<th>Low</th>
<th>Important</th>
<th>Critical</th>
<th>Catastrophic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent</td>
<td></td>
<td>R6a, R6b, R6c, R6d, R8b, R15b, R17b, R20a, R22</td>
<td>R2a, R2c2, R2e, R4a, R4b, R4c, R4d, R4e, R4f, R12a, R13b1, R13b2, R13c1, R14, R15a, R15c, R15d, R15e, R17a, R17c, R20b, R20c, R21b, R23, R24b, R293a, R295a, R31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td>R1a, R3a, R3b, R26b</td>
<td>R1c, R2c1, R2d, R26a,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasional</td>
<td></td>
<td>R27, R29, R293b</td>
<td>R1b, R8a, R13a, R13c2, R21a, R24a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
<td>R27, R29, R293b</td>
<td>R1b, R8a, R13a, R13c2, R21a, R24a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td></td>
<td>R6a, R17b</td>
<td>R1b</td>
<td>R1a, R2b1, R2c2, R13c1, R13c2, R15d-e, R24a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After risk management analysis:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Severity</th>
<th>Negligible</th>
<th>Low</th>
<th>Important</th>
<th>Critical</th>
<th>Catastrophic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent</td>
<td></td>
<td>R6a, R6b, R6c, R6d, R8b, R15b, R17b, R20a, R22</td>
<td>R2a, R2c2, R2e, R4a, R4b, R4c, R4d, R4e, R4f, R12a, R13b1, R13b2, R13c1, R14, R15a, R15c, R15d, R15e, R17a, R17c, R20b, R20c, R21b, R23, R24b, R293a, R295a, R31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td>R1a, R3a, R3b, R26b</td>
<td>R1c, R2c1, R2d</td>
<td>R26a,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasional</td>
<td></td>
<td>R27, R29, R293b</td>
<td>R1b, R8a, R13a, R13c2, R21a, R24a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
<td>R27, R29-4</td>
<td>R3a, R3b, R4a, R4b, R4c, R4d, R4e, R4f, R13b2, R14, R15c, R17a, R17c, R20b, R20c, R21b, R23, R24b, R29-3, R29-5, R31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td></td>
<td>R6a, R17b</td>
<td>R1b</td>
<td>R1a, R2b1, R2c2, R13c1, R13c2, R15d-e, R24a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment:

The application of the means of checking of all identified risks has the effect of bringing the highest of them in the zone “ALARP”.

The zone «Rare - Critical» regroup between 1/3 and the half of residual risks; is explained by the invasive character of the act, the implantable character linked to the zone of establishment of DISCOGEL®. Weak case is supported due to the fact that the "target" practitioners are qualified for interventions in neuroradiology, and due to the fact that training is given to each of them, during the first use, by an experienced surgeon.
9.3. Medical device vigilance records on the 07/06/2013

<table>
<thead>
<tr>
<th>Number of medical device vigilance case</th>
<th>Country of origin</th>
<th>Product responsibility</th>
<th>Product recall</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Romania</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#2</td>
<td>France</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#3</td>
<td>Spain</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#4</td>
<td>France</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

9.4. Conclusion of risks analysis:

**DISCOGEL**® calls an injection technology fluently used in the treatment of the pathologies of the spine. Inherent risks in this gesture are controlled by the skills of the practitioners who implement it.

The ethanol has been used for the treatment of herniated discs pathologies for several years, by bringing an alternative in the treatment by the chymopapaine.

The undesirable effects drawn away, in certain cases, by the use of pure ethanol, under liquid form, (migration of the ethanol at the level of fissure epidural, causing a burn feeling at the level of lower limb) are solved by presentation in form of gel.

The presence of a radio-opaque compound in **DISCOGEL**® allows controlling any possible migration.

Results show that all the residual risks taken independently or in a cumulative way are considered as acceptable with regard to benefits brought to the patient

**DISCOGEL**® allows a substantial reduction of risks and undesirable side effects of the currently available treatments for the treatment of slipped discs.

**THE RATIO BENEFITS VS RISKS IS CONSIDERED AS WIDELY ACCEPTABLE, WITH REGARD TO OTHER CURRENTLY AVAILABLE OPTIONS FOR THE TREATMENT OF HERNIATED DISCS.**

This risk analysis has been performed by Michaël LEBAIL, CEO of **GELSCOM** with the help of a company called CEISO, which is specialized in CE marking.

10. Material Specifications

Certificate called batch realize certificate is sent to the local distributor once all the analysis performed comply with the specifications of analysis on finished product here after:

We, manufacturer, signed and stamped all documents, which are attached and here by certify the information provided on this application and in any attached documentation is correct, complete and guarantee the quality of the products is exported to Iran. If any false data are found, we assume legal responsibility, and hold responsibility for all the consequences arising thereafter and this is grounds for refusal to issue registration certificate.

Name of signing official: Michaël LE BAIL, CEO of **GELSCOM SAS**

Dated on the 8th of June 2013
11. Annexes
Annex 1: labeling material

- Outer box of the kit (size 290mm x 60 mm x 30mm):

Made in France
• Label of the vial (example given for batch D0033)

![Label Image]

• Traceability flag labels to be sticker on each patient’s medical dossier

3 flag labels per kit:

- One on the outer box
- Two inside the box
Annex 2: Instruction for use (recto & verso)
Annex 3: Quality management certificate

GRAND-DUCHE DE LUXEMBOURG

Société Nationale de Certification et d’Homologation s.à.r.l.

Quality Management System Certificate
Certificat de Système de Management de la Qualité
Zertifikat eines Qualitätsmanagementsystems

We hereby certify that the Quality Management System of the organization
Nous certifions par la présente que le système de management de la qualité de l’organisme
Wir bestätigen hiermit, daß das Qualitätsmanagementsystem der Organisation

GELSCOM SAS
8, avenue de Dubna
ZAC CITIS 1
FR-14200 HEROUVILLE SAINT CLAIR

is in conformity with the requirements of the following standards:
est conforme aux exigences des normes suivantes:
den Anforderungen der folgenden Normen entspricht:

EN ISO 13485:2003
(Exclusions / Ausschlüsse: 7.3, 7.5.1.2.2, 7.5.1.2.3, 7.5.4)

for the scope:
pour le domaine d’application:
für den Anwendungsbereich:

Fabrication et mise sur le marché de solutions à base d’éthanol gélifié pour
application médicale
Manufacturing and sales of solutions based on jellified ethanol for medical
application

Certificate No.: 1144635-00
Valid until: 2015-01-01

The present certificate is subjected to a yearly surveillance.
Le présent certificat est soumis à une surveillance annuelle.
Das vorliegende Zertifikat unterliegt einer jährlichen Überwachung.

Société par Actions Simplifiée au capital de 100 000€
RCS CAEN n°483 156 071 (2010B375)
Version v3.0
Annex 4: CE approval

GRAND-DUCHE DE LUXEMBOURG

Société Nationale de Certification et d’Homologation s.a.r.l.

Notified Body
Organisme Notifié - Benanne Stelle
N° 0499

Annex to Certificate No.:
Annexe au certificat no.:
Anhang zur Bescheinigung Nr.:

1144634-01

Manufacturer:
Fabricant / Hersteller:

GELSCOM SAS

Scope:
Domaine d’application:
Zweckbestimmung:

Manufacture and final inspection
Fabrication et contrôle final
Fertigung und Endkontrolle

Device Identification:
Identification du dispositif:
Produktidentifizierung:

Ethanol gelifie destine au traitement des cavités angiomateuses à bas débit sanguin
Ethanol gel for treatment of low-flow vascular malformations
SCLEROGEL®

Dispositif medical sterile destine au traitement des hernies discales intervertébrales
Sterile medical device to treat intervertebral disc hernia
DISCOGEL

GMDN:
not available / non disponible / nicht verfügbar

This annex is only valid if attached to the certificate mentioned above.
La présente annexe est seulement valable en relation avec le certificat mentionné ci-dessus.
Dieser Anhang hat nur Gültigkeit in Verbindung mit der oben genannten Bescheinigung.

Luxembourg, 2012-07-23

Claude UIESCH
Directeur
GRAND-DUCHE DE LUXEMBOURG

Société Nationale de Certification et d’Homologation s.à r.l.

Notified Body
Organisme Notifié - Benannte Stelle
N° 0499

EC Type Examination Certificate
Certificat d’examen CE de type - EG-Baumusterprüfbescheinigung

according to Annex III of directive 93/42/EEC on Medical Devices
conformément à l’Annexe III de la Directive 93/42/CEE relative aux dispositifs médicaux
gemäß Anhang III der Richtlinie 93/42/EWG über Medizinprodukte

Manufacturer:
Fabricant:
Hersteller:

GELSCOM SAS
8, avenue de Dubna
ZAC CITIS 1
FR-14200 HEROUVILLE SAINT CLAIR

Certificate No.:
No. du certificat:
Bescheinigung Nr.:

1244783-00
Valid until:
Validé jusqu’au:
Gültig bis:

2017-09-27

Device Identification:
Identification du dispositif :
Produktidentifizierung:

Dispositif médical stéré de traitement des hernies discales intervertébrales
Sterile medical device to treat intervertebral disc hernia

DISCOGEL®

GMDN:
not available / non disponible / nicht verfügbar

We hereby declare that a type examination has been carried out on the listed device(s) in accordance with the requirements of Annex III (4) of the Directive 93/42/EEC on medical devices. We certify that the type conforms to the relevant provisions of the aforementioned directive.

Nous déclarons qu’un examen de type du/des dispositif(s) mentionné(s) a été réalisé selon les exigences de l’Annexe III (4) de la Directive 93/42/CEE relative aux dispositifs médicaux. Nous certifions que le type est conforme aux exigences applicables de la Directive mentionnée ci-dessus.

Hiermit bestätigen wir, daß ein Baumuster der aufgelisteten Produkte geprüft wurde gemäß den Anforderungen des Anhangs III (4) der Richtlinie 93/42/EWG über Medizinprodukte. Wir bescheinigen, daß das Baumuster den anwendbaren Bestimmungen der oben erwähnten Richtlinie entspricht.

Luxembourg, 2012-09-28

Claude LIESCH
Directeur
Société Gelscom SAS - 8, avenue de Dubna - ZAC CITIS 14200 Hérouville-Saint-Clair - FRANCE
Tel : +33 2 31 94 90 29 - Fax : +33 2 22 06 33 42 - email : contact@gelscom.com / Website : www.gelscom.com

GRAND-DUCHE DE LUXEMBOURG

Société Nationale de
Certification et d’Homologation s.a.r.l.

Notified Body
Organisme Notifié - Benannte Stelle
N° 0499

EC Certificate - Production Quality Assurance System
Certificat CE - Système d’assurance de la qualité de la fabrication
EG-Bescheinigung - Produktions-Qualitätsicherungssystem

according to Annex V of directive 93/42/EEC on Medical Devices
conformément à l’Annexe V de la Directive 93/42/CEE relative aux dispositifs médicaux
gemäß Anhang V der Richtlinie 93/42/EWG über Medizinprodukte

Manufacturer:
GELS.COM SAS
8, avenue de Dubna
ZAC CITIS 1
FR-14200 HEROUVILLE SAINT CLAIR

Certificate No.:
1144634-01
Valid until:
2017-01-01

Date of last audit:
2012-03-09

Scope:
see annex to this certificate
voir l’annexe de ce certificat

We hereby declare that the manufacturer’s quality system was audited in accordance with the requirements of Annex V of the Directive 93/42/EEC on medical devices. We certify that the quality system meets the requirements of the aforementioned directive.


Hiermit bestätigen wir, daß das Qualitätsystem des Herstellers auditiert wurde gemäß den Anforderungen des Anhangs V der Richtlinie 93/42/EWG über Medizinprodukte. Wir bescheinigen, daß das Qualitätsystem den Vorgaben der oben erwähnten Richtlinie entspricht.

RCS CAEN n°483 156 071 (2010B375)

Version v3.0