ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Spherox 10-70 spheroids/cm² implantation suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Spheroids of human autologous matrix-associated chondrocytes for implantation suspended in isotonic sodium chloride solution.

2.2 Qualitative and quantitative composition

Spheroids are spherical aggregates of \textit{ex vivo} expanded human autologous chondrocytes and self-synthesized extracellular matrix.

Each pre-filled syringe or applicator contains a specific number of spheroids according to the defect size (10-70 spheroids/cm²) to be treated.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Implantation suspension.

White to yellowish spheroids of matrix-associated autologous chondrocytes in a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Repair Society [ICRS] grade III or IV) with defect sizes up to 10 cm² in adults.

4.2 Posology and method of administration

Spherox is intended for autologous use only. It must be administered by an appropriately qualified physician and in a medical facility.

Posology

10-70 spheroids are applied per square centimetre defect.

\textit{Paediatric population}

The safety and efficacy of Spherox in children aged 15 to 18 years have not been established.
The safety and efficacy of Spherox in children aged less than 15 years have not been established. No data are available.

Elderly
The safety and efficacy of Spherox in patients aged over 50 years have not been established. No data are available.

Method of administration

For intraarticular use.

Spherox is administered to patients by intraarticular implantation.

The implantation must be performed during a surgical procedure (preferably an arthroscopy or mini-arthrotomy). A debridement of the defect area is required. The subchondral plate should not be damaged. The spheroids are provided in a pre-filled syringe or an applicator (stem length 150 mm (co.fix 150)). Spheroids should be applied evenly on the defect ground and, if necessary, spread over the whole defect area by means of surgical instruments. The spheroids self-adhere within 20 minutes onto the defect ground. Afterwards, the surgical wound can be closed without any additional cover of the treated area (e.g. periosteal flap), or any fixation of spheroids by using fibrin glue. The treatment of defect sizes up to 10 cm² is eligible for single as well as adjacent defects (combined area).

Patients treated with Spherox have to undergo a specific rehabilitation program (see section 4.4). The program may take up to one year depending on the recommendation of the physician.

For information on preparation and handling of Spherox, please refer to section 6.6.

4.3 Contraindications

- Patients with not fully closed epiphyseal growth plate in the affected joint.
- Primary (generalised) osteoarthritis.
- Advanced osteoarthritis of the affected joint (exceeding grade II according to Kellgren and Lawrence).
- Infection with the hepatitis B virus (HBV), hepatitis C virus (HCV) or HIV I/II viruses.

4.4 Special warnings and precautions for use

General

Spherox is an autologous medicinal product and must not be given to any other patient than the donor.

Prior to use, it must be verified if patient name matches the information of the patient/donor provided on the shipping documents and the product label. Also it needs to be checked if the correct order number (lot number) is on the primary package.

If the primary or secondary packaging is damaged and therefore unsterile, Spherox must not be applied.

The application of Spherox in patients with cartilage defects outside the knee joint is not recommended. The safety and efficacy of Spherox in patients with cartilage defects outside the femoral condyle and the patella of the knee have not been established. No data are available.

Precautions for use

Patients with local inflammations or acute as well as recent bone or joint infections should be temporarily deferred until the recovery from the infection is documented.
In the pivotal studies of Spherox, patients were excluded if they had signs of chronic inflammatory diseases.

Concomitant joint problems like early osteoarthritis, subchondral cartilage defects, instability of the joint, lesions of ligaments or of the meniscus, abnormal weight distribution in the joint, varus or valgus malalignment, patellar malalignment, and metabolic, inflammatory, immunological or neoplastic diseases of the affected joint are potential complicating factors. Untreated bone oedema corresponding with the cartilage defect to be treated may adversely affect the success of the procedure. If possible, concomitant joint problems should be corrected prior to or at the latest at the time of Spherox implantation.

For decision on treatment of facing defects (“kissing lesions” larger than ICRS grade II) the degree of overlap and location of the defects in the joint have to be taken into consideration.

Post-operative haemarthrosis occurs mainly in patients with a predisposition to haemorrhage or poor surgical haemorrhage control. The patient’s haemostatic functions should be screened prior to surgery. Thromboprophylaxis should be administered according to local guidelines.

Application of Spherox in obese patients is not recommended.

**Rehabilitation**

After implantation, the patient should follow an appropriate rehabilitation schedule. Physical activity should be resumed as recommended by the physician. Too early and vigorous activity may compromise the grafting and the durability of clinical benefit from Spherox.

Compliance with an adequate rehabilitation programme after implantation (especially for patients with mental disorders or addiction) should be warranted.

**Cases in which Spherox cannot be supplied**

If the manufacturing of spheroids has failed or if the release criteria are not fulfilled, e.g. due to insufficient biopsy quality, the medicinal product cannot be delivered. The physician will be informed immediately.

**4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed. Locally applied antibiotics or disinfectants may have potential toxicity on articular cartilage and it is not recommended that Spherox comes into direct contact with those substances. In the pivotal studies of Spherox, patients were excluded if they were under medical treatment with corticosteroids.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy and breast-feeding**

No clinical data on exposed pregnancies are available for autologous chondrocytes or spheroids from autologous chondrocytes. As Spherox is used to repair cartilage defects of the joint and is therefore implanted during a surgical procedure, it is not recommended for use in pregnant or breast-feeding women.

**Fertility**

There are no data on possible effects of Spherox treatment on fertility.
4.7 Effects on ability to drive and use machines

Due to the surgical nature of the underlying procedure, implantation of Spherox has a major influence on the ability to drive and use machines. During the rehabilitation period, this ability can be restricted due to reduced mobility. Therefore, patients should consult their treating physician and follow his/her advice strictly.

4.8 Undesirable effects

Summary of safety profile

During treatment with Spherox adverse reactions associated with the surgical procedure (implantation) or associated with Spherox may occur.

Adverse reactions associated with Spherox
- Graft delamination
- Hypertrophy

Adverse reactions associated with joint surgery
- Joint effusion
- Arthralgia

Tabulated list of adverse reactions

Information on adverse reactions in 177 patients from pivotal clinical trials are available. Furthermore, adverse reactions obtained from queries of the treating surgeons as well as from spontaneous reports were considered.

The adverse reactions are displayed by system organ class and frequency in Table 1 below: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Common</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>Haematoma, Thrombophlebitis superficial, Deep vein thrombosis, Lymphoedema</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Very common</td>
<td>Joint effusion, Arthralgia, Joint swelling</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Muscular weakness, Joint lock, Joint crepitation, Chondropathy, Tendonitis</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Hypertrophy, Chondromalacia, Synovial cyst</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Gait disturbance, Pain</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Discomfort</td>
</tr>
<tr>
<td>Injuries, poisoning and</td>
<td>Common</td>
<td>Meniscus injury,</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>procedural complications</td>
<td>Uncommon</td>
<td>Suture-related complication, Graft delamination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ligament sprain</td>
</tr>
</tbody>
</table>

Description of selected adverse reactions

**Graft delamination**

Graft delamination describes the partial or complete detachment of the formed tissue from the subchondral bone and the surrounding cartilage. A complete graft delamination is a serious complication which can be accompanied by pain. Risk factors are in particular non-treatment of concomitant diseases, such as subchondral bone oedema.

**Hypertrophy of the transplant**

A symptomatic hypertrophy of the transplant may occur during treatment with Spherox resulting in pain.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 **Overdose**

In cases where the recommended dose was significantly exceeded (up to 170 spheroids/cm² in an investigator-initiated trial with a follow-up period of 12 months), no negative effects were observed.

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Other drugs for disorders of the musculo-skeletal system, ATC code: M09AX02

**Mechanism of action**

Autologous chondrocyte implantation (ACI) is based on the removal of the patient’s own chondrocytes isolated from healthy cartilage, their culture *in vitro* and their subsequent implantation into the cartilage defect. Spherox is cultured and implanted as three-dimensional spheroids.

**Clinical efficacy**

Since 2004, Spherox has been available on a named patient basis for the treatment of cartilage defects classified as Outerbridge grade 3 or 4 or ICRS grade III or IV (Outerbridge 1961, ICRS Cartilage Injury Evaluation Package 2000). Mainly, patients were treated with cartilage defects in knee.

Spherox has been analysed in a prospective, randomized, uncontrolled open-label, multicentre Phase II clinical study including 75 patients with focal cartilage defects (ICRS grade III or IV) in the knee with a defect size of 4-10 cm². Twenty-five patients were treated with 10-30 spheroids/cm² defect, 25 with 40-70 spheroids/cm² defect and 25 with 3-7 spheroids/cm² defect. The mean patient age was 34 years (range 19 to 48 years) with a mean body mass index (BMI) of 25.2. In all 3 dose groups a significant improvement (*p* < 0.05) of the KOOS (Knee Injury and Osteoarthritis Outcome Score) after 12, 24 and 36 months compared to before treatment could be observed. For ‘all dose groups’ the mean overall KOOS rose in the first year after treatment from 57.0 to 73.4 on a scale from 0 (worst) to 100 (best)
and continued to rise slightly, reaching 74.6 after 18 months, 73.8 after two years and 77.0 after three years. Changes within each dose group were of similar magnitude, and the three between-group (pairwise) analyses did not reveal any statistically significant differences between the groups. Further patient scores, e.g. the International Knee Documentation Committee (IKDC; subjective evaluation of the knee) and the Lysholm score showed after 12, 24 and 36 months also a significant improvement in comparison to the value before treatment.

Magnetic resonance imaging (MRI) results according to the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring system (0 = worst result; 100 = best result) showed an improvement within the first 36 months from 59.8 at Visit 2 (3 months after treatment) up to 72.4 points in the group of patients treated with 3-7 spheroids/cm² defect, from 64.5 at Visit 2 up to 79.6 points in the dose group of 10-30 spheroids/cm² defect, and from 64.7 at Visit 2 up to 72.1 points in the dose group of 40-70 spheroids/cm² defect.

Currently, a multicentre, prospective, randomised, controlled clinical Phase III study is ongoing. The objective of the study is to compare the efficacy and safety of the treatment of cartilage defects (1 to less than 4 cm²) at the femoral condyle of the knee joint with Spherox and microfracture treatment over a period of 5 years. The final statistical assessment will be 24 months after treatment. The current interim analysis 12 months after treatment reveals data as follows:

The treatment groups were balanced with respect to size, demography and disease background. The analysis population comprised 102 patients (41 women, 61 men) aged 37 years on average (range from 18 to 49 years) with a mean body mass index (BMI) of 25.8. Defect sizes ranged from 0.5 to 4 cm². ICRS grades were mostly IV A, followed by IIIB and IIIA (56, 23 and 10 patients respectively). None of the patients had received prior treatment with microfracture for their lesion.

As part of the interim analysis, the assessment of the ‘overall KOOS’ for the intention-to-treat (ITT) population showed that both treatments yielded a statistically significant improvement relative to baseline. For the patients treated with Spherox the mean overall KOOS (scale of 0-100) increased from 56.6 ± 15.4 at baseline to 78.7 ± 18.6 at the follow-up visit 12 months after treatment. For patients treated by microfracture the mean overall KOOS increased from 51.7 ± 16.5 to 68.1 ± 18.6 (p < 0.0001 in both cases). With regard to the between-group analysis, the treatment with Spherox passed the test of non-inferiority compared with microfracture (Δ of 5.7 with lower bound of CI equal to –1.0). MOCART scores of 67 and 62 for the Spherox and microfracture groups at follow-up visit 3 months after treatment, improved to 81 and 77 at 12 months after treatment (0 = worst result; 100 = best result).

IKDC subscores as well as results from the IKDC Current Health Assessment Form and the modified Lysholm score also revealed overall improvements from baseline in both treatment groups with numerically slightly better results in the Spherox group but with no statistical significance.

5.2 Pharmacokinetic properties

Due to the nature and intended clinical use of Spherox, conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable.

5.3 Preclinical safety data

Ex vivo produced spheroids were implanted in mice (subcutaneous implantation of cartilage explants with human spheroids) or in minipigs (autologous spheroids implanted in cartilage defects). No signs of inflammation, synovitis, infections, rejection, hypertrophy or immune toxicity, tumourigenicity or biodistribution were observed.

A GLP-compliant examination of biodistribution and tumourigenicity in NSG mice showed no signs of biodistribution and/or migration from implanted human spheroids. No suspicion of potential tumourigenesis or increased prevalence of tumours due to the implanted spheroids was observed. In a sheep study, also no biodistribution was observed after injection of spheroids into the knee joint. This suggests that there are no risks for the use of spheroids in humans.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

6.2 Incompatibilities

In absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

6.3 Shelf life

72 hours

6.4 Special precautions for storage

Store at temperatures between 1 °C and 10 °C.
Do not freeze.
Do not irradiate.
Do not open the outer packaging before use to prevent microbial contamination.

6.5 Nature and contents of container and special equipment for use, administration or implantation

The spheroids are provided in an applicator or a pre-filled syringe as primary packaging unit.

The applicator (stem length 150 mm (co.fix 150)) is packed in a sterile tube and additionally surrounded by an extra bag. A tube may contain a maximum of two co.fix 150. The catheter of the applicator is made of thermoplastic polyurethane, the sealing plug on one side of acrylonitrile butadiene styrene and a silicone stopper on the other side. The applicator is delivered with an application device (sterile injection syringe).

The pre-filled syringe consists of a luer lock, a sealing ring and a cover cap. It is packed in a sterile tube with a screw-type cap and additionally surrounded by an extra bag. All parts of the pre-filled syringe are made of polypropylene, the sealing ring of isoprene. Silicone oil serves as lubricant. The pre-filled syringe is delivered with an application device (indwelling cannula or filter stem).

Pack sizes

The number of primary packaging units delivered depends on the type of the primary packaging unit and the number of spheroids necessary for the specific defect size (10-70 spheroids/cm²).

One applicator has a maximum capacity of 60 spheroids in a volume of up to 200 microlitre isotonic sodium chloride solution.
One pre-filled syringe has a maximum capacity of 100 spheroids in a volume of up to 1000 microlitre isotonic sodium chloride solution.

6.6 Special precautions for disposal and other handling

If the primary or secondary packaging is damaged and therefore unsterile, Spherox should not be applied.

Remaining spheroids must not be stored for later application.
Any unused product or waste material should be disposed in accordance with local requirements.
7. MARKETING AUTHORISATION HOLDER

CO.DON AG
Warthestraße 21
14513 Teltow
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1181/001
EU/1/17/1181/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

CO.DON AG
Warthestr. 21
14513 Teltow
GERMANY

Name and address of the manufacturer responsible for batch release

CO.DON AG
Warthestr. 21
14513 Teltow
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal. The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

• At the request of the European Medicines Agency;
• Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

• Additional risk minimisation measures

Prior to launch of Spherox in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the training programme and the controlled distribution
programme, including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authority.

The main objectives of the educational programme are to provide training to surgeons and other health professionals on proper procurement, storage, handling and administration of Spherox.

The MAH shall ensure that in each Member State where Spherox is marketed, all surgeons and other health professionals who are expected to prescribe and administer the product have access to the educational materials including:

- The Summary of Product Characteristics
- Training materials for surgeons and training materials for other health professionals
- Prescriber checklist
- Forms for documentation

- The training material for surgeons and surgical staff shall contain the following key elements:
  - Information on Spherox, including the indication currently approved and legal basis
  - Detailed description of the biopsy harvest procedure and the administration procedure, the implantation by knee-joint arthrotomy and the follow-up protocol
  - Preparation of the patient for the procedure and subsequent monitoring
  - The need to officially confirm that training has been conducted prior to the biopsy.
  - The importance to complete the checklist
  - Recommendations on rehabilitation post biopsy and post transplantation

- The training material for other health professionals shall contain the following key elements:
  - Information on Spherox, including the indication currently approved and legal basis
  - The need to screen donors for hepatitis B, hepatitis C, HIV and syphilis
  - Detailed description of the handling of the biopsy harvest and of the product, elements on the preparation for the implantation, the schedule for the patient follow-up and recommended physiotherapy.
  - The need to officially confirm that training has been conducted prior to the biopsy.

- The Prescriber checklist shall contain the following key messages:
  - Corroboration that the patient receiving the product is the right patient receiving the appropriate product
  - Confirmation of the appropriate side of the implantation
  - A reference to the fact that the patient has been informed and understands the benefits and risks of the product and the associated procedures

The MAH shall ensure that in each Member State where Spherox is marketed, a system aimed to control access to the product beyond the level of control ensured by routine risk minimisation measures. The following requirements need to be fulfilled before the product is prescribed and dispensed:
• Specific testing and examination of the patient to ensure compliance with strictly defined clinical criteria
• The patient should document the receipt and understanding of the information on the product
• The product will only be available to surgeons certified to prescribe and administer Spherox
• Measures to ensure the traceability of the product and guarantee the identification of: patient data; diagnosis leading to the treatment; information on biopsy including date of the operation, adverse events reported during the procedure and quality of the biopsy; information on the implant, including all in-process controls and final product controls.

• **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
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</table>
| Post-authorisation efficacy study (PAES): 60-month follow-up data for study cod 16 HS 13. In order to evaluate the long-term efficacy and safety of Spherox vs. microfracture in patients with cartilage defects of the knee with a defect size between 1 and < 4 cm², the MAH should conduct and submit the results of the ongoing prospective, randomised, open label, multicentre study. | Interim reports:  
To be submitted annually  
Final study report: 01-Mar-2021 |
| To conduct a prospective process validation study post marketing using batches manufactured with a well-controlled process and to collect quality data from a sufficient number of batches to demonstrate consistency, quality and genetic stability of the cells in the finished product. On the basis of the process validation study, in process controls should be reviewed and the acceptance criteria tightened accordingly for the manufacturing process for P0 culture time, total ML culture time, spheroid culture time and amount of synovial impurities. | April 2019 |
| To re-validate the potency assay post marketing and to monitor its correlation with the efficacy outcome. | March 2018 |
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Pouch

1. NAME OF THE MEDICINAL PRODUCT

Spherox 10-70 spheroids/cm² implantation suspension
spheroids of human autologous matrix-associated chondrocytes

2. STATEMENT OF ACTIVE SUBSTANCE(S)

This medicine contains a specific number of spheroids of human autologous matrix-associated chondrocytes according to the defect size (10-70 spheroids/cm²).

3. LIST OF EXCIPIENTS

Excipient: sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Implantation suspension,
In case of application system co.fix 150 mm as primary packaging unit:
{1 or 2} application system{s} co.fix 150 mm containing {Number of Spheroids} spheroids in a sterile tube

In case of syringe as primary packaging unit:
1 syringe containing {Number of Spheroids} spheroids in a sterile tube

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intraarticular use

Read the package leaflet before use;

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.
8. EXPIRY DATE

EXP {DD month YYYY} at {hours} CET

9. SPECIAL STORAGE CONDITIONS

Store between 1 °C and 10 °C, do not freeze, do not irradiate, do not open the outer packaging before use to prevent microbial contamination.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CO.DON AG, Warthestraße 21, 14513 Teltow, Germany
Tel: +49 (0)3328 43 46 0, Fax: +49 (0)3328 43 46 43, Email: info@codon.de

12. MARKETING AUTHORISATION NUMBER(S)

In case of application system co.fix 150 mm as primary packaging unit:
EU/1/17/1181/001

In case of syringe as primary packaging unit:
EU/1/17/1181/002

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Pt Name, Pt ID: {Patient Name}, {Patient ID}
Lot {Batch Number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.
18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.
## PARTICULARS TO APPEAR ON THE SECONDARY PACKAGING

**Tube**

Application system co.fix 150 mm
or
Syringe

### 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Spherox 10–70 spheroids/cm² implantation suspension

### 2. METHOD OF ADMINISTRATION

For intraarticular use

### 3. EXPIRY DATE

EXP {DD month YYYY} at {hours} CET

### 4. BATCH NUMBER, DONATION AND PRODUCT CODES

{Patient ID (including the Batch Number)}

### 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

*In case of application system co.fix 150 mm as primary packaging unit:*

{1 or 2} application system{s} co.fix 150 mm in a sterile tube

*In case of syringe as primary packaging unit:*

1 syringe in a sterile tube

### 6. OTHER

For autologous use only.
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**Application system co.fix 150 mm**

or

**Syringe**

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<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application system co.fix 150 mm:</strong></td>
</tr>
<tr>
<td>Spherox 10–70 spheroids/cm² implantation suspension</td>
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<tr>
<td><strong>Syringe:</strong></td>
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<td>Spherox 10–70 spheroids/cm² implantation suspension</td>
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<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>For intraarticular use</td>
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<tr>
<th>3. EXPIRY DATE</th>
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<td><strong>Application system co.fix 150 mm:</strong></td>
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<td>EXP {DD month YYYY} at {hours} CET</td>
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<tr>
<td><strong>Syringe:</strong></td>
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<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<tbody>
<tr>
<td>{Number of spheroids} sph</td>
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<tr>
<th>6. OTHER</th>
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<tbody>
<tr>
<td>For autologous use only.</td>
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</table>
B. PACKAGE LEAFLET
This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given with this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor or physical therapist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Spherox is and what it is used for
2. What you need to know before you are given Spherox
3. How to use Spherox
4. Possible side effects
5. How to store Spherox
6. Contents of the pack and other information

1. What Spherox is and what it is used for

Spherox consists of so-called spheroids. A spheroid looks like a tiny pearl made of cartilage cells and cartilage material derived from your own body. Cartilage tissue is present in every joint as a hard smooth layer on the surface of bone ends. It protects the bones and allows our joints to work smoothly. To make the spheroids, a small cartilage sample is taken from part of one of your joints during a minor operation, and then grown in the laboratory to make the medicine. By surgery the spheroids are implanted to the defected cartilage area and stick to the defect site. They are then expected to repair the defect with healthy and functional cartilage over time.

Spherox is used to repair cartilage defects of knee in adults. These defects can be caused by acute injury, such as a fall. They can also be caused by repetitive injury, such as long-term incorrect weight bearing on the joint. Spherox is used to treat defects up to 10 cm² in size.

2. What you need to know before you are given Spherox

Do not use Spherox if

- the bones in the joint have not finished growing
- you have advanced joint and bone inflammation with degeneration in the affected joint (osteoarthritis)
- you are infected with HIV (the virus that causes AIDS), hepatitits B virus or with hepatitis C virus

Warnings and precautions

Talk to your doctor before you are given Spherox, if you have any other joint problems or excess weight, as this may reduce the success of the procedure.
Spherox should preferably be implanted into an otherwise healthy joint. Other joint problems should be corrected before or at the time of Spherox implantation.

Rehabilitation program

Follow the rehabilitation program, strictly, after implantation. **Only resume physical activity when instructed** by your doctor. Resuming vigorous activity too soon may reduce the benefit and durability of Spherox.

Other cases in which Spherox cannot be supplied

Even if the cartilage sample has already been taken, it may happen that you cannot be treated with Spherox. This can occur because the sample taken is not of sufficient quality to manufacture the product. Your doctor might have to select an alternative treatment for you.

**Children and adolescents**

Spherox is **not recommended** in children or adolescents below 18 years.

**Other medicines and Spherox**

Tell your doctor if you are using, have recently used or might use any other medicines.

**Pregnancy and breast-feeding**

Spherox is **not recommended** for pregnant or breast-feeding women, as it is applied during surgery. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

**Driving and using machines**

The surgical procedure will have a major influence on your ability to drive and use machines. Driving cars and using machines may be limited during the rehabilitation period. Strictly follow the advice of your doctor or physical therapist.

**3. How to use Spherox**

Spherox can only be implanted by a specialist doctor in a medical facility and must only be used in the patient for whom it has been prepared.

The treatment of adults and full-grown adolescents with Spherox is a two-step procedure:

**Visit 1:**
**Evaluation of the cartilage defect, sample and blood taking**

On the first visit, the doctor will evaluate your cartilage defect during an exploratory operation. This is usually done as keyhole surgery through very small incisions (cuts), using a special instrument to look inside the knee (arthroscopy).

If Spherox is appropriate for you, the doctor takes a small **cartilage sample from your joint**. Your cartilage cells are extracted from this sample in a laboratory and are then grown to make the spheroids that constitute Spherox. The process takes about 6 to 8 weeks.
Visit 2:  
**Spherox implantation**

Spherox is implanted into the cartilage defect in the joint during the next operation. This may also be carried out by keyhole surgery.

**Rehabilitation**

In order to allow your joint to recover well, you will have to follow an individual rehabilitation program. This may take up to one year. Your doctor or physical therapist will advise you.

**Very important:** Carefully comply with the recommendations of your doctor and physical therapist. The risk of treatment failure may increase if you do not follow your rehabilitation schedule. Be very careful when bending and putting weight on your treated joint. During the rehabilitation period, the amount of weight you can put on the joint will increase gradually. How quickly this occurs depends for example on your body weight and the size of the cartilage defect. Depending on the treated joint, you may have to wear a brace.

Ask your doctor or physical therapist if you have any further questions about treatment with Spherox.

4. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. Side effects appearing after the implantation of Spherox are mostly related to the surgery. In general, these side effects are quite mild and disappear during the weeks following surgery.

**If you get any of the following serious side effects, you should immediately contact a doctor:**

- hypersensitivity (allergy) (symptoms: e.g. skin reactions, low blood pressure, constriction of airways, swollen tongue or throat, weak and rapid pulse, sickness, vomiting, diarrhoea, dizziness, fainting, fever)
- blood clot in a deep vein (symptoms: e.g. swelling, pain, increased warmth in the affected area)

**Other side effects**

Side effects can occur with the following frequencies:

**Very common:** may affect more than 1 in 10 people
- accumulation of fluid in the joint
- pain in the joint
- swelling in the joint

**Common:** may affect up to 1 in 10 people
- muscle weakness
- joint lock
- cracking sounds in the joint
- regression of cartilage
- tendon inflammation
- impairment of walking
- meniscus injury
- ligament disorder
- pain
Uncommon: may affect up to 1 in 100 people

- increase in size of the cartilage cells
- softening of cartilage
- tissue lump that may occur in the joint
- uneasiness
- wound-related complication
- partial or complete detachment of the tissue beneath the bone and surrounding cartilage
- internal bleedings
- inflammation of veins combined with the formation of a blood clot located near the surface of the skin (symptoms: e.g. redness and/or warmth of the skin along the vein, tenderness, pain)
- swelling due to obstructed flow of tissue fluid via the lymph vessels
- increased heartbeat

Reporting side effects

If you get any side effects, talk to your doctor or physical therapist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Spherox

Do not use this medicine after the expiry date which is stated on the label after EXP. Store and transport refrigerated (1 °C to 10 °C). Do not freeze. Do not irradiate. Do not open the outer packaging before use to prevent microbial contamination.

6. Contents of the pack and other information

What Spherox contains

- The active substance of Spherox are spheroids that consist of cartilage cells and cartilage material derived from your own body.
  Spherox contains 10-70 spheroids per cm² of the cartilage defect.
- The other ingredient is sodium chloride used as transport solution.

What Spherox looks like and contents of the package

Implantation suspension.

Spherox contains so-called spheroids that consist of living cartilage cells with a non-cellular portion for the repair of cartilage defects. The spheroids look like small white to yellowish pearls. They are transported in a clear colourless solution. Spherox is delivered to the doctor in a container ready for application. The container may be a syringe or a special application system called co.fix. This is a catheter with a stem length of 150 mm. The container used varies, depending on the doctor’s preference. The applicator co.fix 150 is packed in a sterile tube and additionally surrounded by an extra bag. The pre-filled syringe is packed in a sterile tube and additionally surrounded by an extra bag.
Marketing Authorisation Holder and Manufacturer

CO.DON AG
Warethstraße 21
14513 Teltow, Germany
Tel.: +49 3328 43460
Fax: +49 3328 434643
E-mail: info@codon.de

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Detailed information on this medicine is available on the European Medicines Agency web site: