ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Spherox 10-70 spheroids/cm^2 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 *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/cm^2) 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 Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2 in adults and adolescents with closed epiphyseal growth plate in the affected joint.

4.2 Posology and method of administration

Spherox is intended for autologous use only. It must be administered by a specialised orthopedic surgeon and in a medical facility.

Posology

10-70 spheroids are applied per square centimetre defect.

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

Paediatric population
The safety and efficacy of Spherox in children and adolescents with still open epiphyseal growth plate in the affected joint have not been established. No data are available.

Method of administration

For intraarticular use.

Spherox is administered to patients by intraarticular implantation.

The treatment with Spherox is a two-step procedure.

In a first step, a biopsy must be performed during a surgical procedure (preferably an arthroscopy or mini-arthrotomy). During arthroscopy or arthrotomy the defect and defect size of the cartilage should be determined as accurately as possible. After biopsy, the cartilage cells will be cultured at the manufacturing site until they will form spheroids that constitute Spherox. The process takes about 6 to 8 weeks.

In a second step, 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; matrix), or any fixation of spheroids by using fibrin glue. The treatment of defect sizes up to 10 cm^2 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 hepatitits B virus (HBV), hepatitis C virus (HCV) or HIV I/II.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years after expiry date of the product.

Autologous use

Spherox is intended solely for autologous medicinal use and should under no circumstances be given to any other patient than the donor. Spherox must not be administered if the information on the product labels and shipping documents do not match the patient’s identity. The order number (lot number) on the primary package should also be checked prior to administration.

General

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

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

Treatment of 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 such as early osteoarthritis, subchondral bone defects, instability of the joint, lesions of ligaments or of the meniscus, abnormal weight distribution in the joint, varus or valgus malalignment, patellar malalignment or instability, 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 a 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 haemostatic functions of the patient 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) is required.

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

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 women.

Breastfeeding

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 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

The surgical procedure (i.e. the biopsy or implantation of Spherox) will have a major influence on the ability to drive and use machines. During the rehabilitation period, the ability to drive and use machines may also be restricted due to reduced mobility. Therefore, patients should consult their treating physician and strictly follow their advice.

4.8 Undesirable effects

Summary of safety profile

Information on adverse reactions from clinical trials and a non-interventional study in adolescents as well as from post-marketing experience are available. During treatment with Spherox surgery-related (implantation) or Spherox-related adverse reactions may occur.

Tabulated list of adverse reactions

The adverse reactions related to Spherox 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 1: Undesirable Effects related to Spherox

System Organ Class (SOC)	Frequency	Adverse Reaction
Infections and infestations	Rare	Cellulitis Osteomyelitis
Immune system disorders	Rare	Hypersensitivity
Musculoskeletal and connective tissue disorders	Common	Bone marrow oedema Joint effusion Arthralgia Joint swelling
	Uncommon	Chondromalacia Joint noise Joint lock Synovial cyst Chondropathy Synovitis Loose body in the joint

System Organ Class (SOC)	Frequency	Adverse Reaction
	Rare	Osteochondrosis Osteonecrosis Osteophyte formation Arthritis infective
	Not known	Arthrofibrosis
General disorders and administration site conditions	Common	Pain
	Uncommon	Gait disturbance
Injury, poisoning and procedural complications	Uncommon	Hypertrophy Graft loss
	Rare	Graft delamination Implant site infection Infrapatellar fat pad inflammation

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 joint instability or lack of compliance with the rehabilitation protocol.

Hypertrophy
A symptomatic implant site hypertrophy may occur during treatment with Spherox resulting in pain.

Adverse reactions related to the surgical procedure:

The following adverse reactions considered surgery-related have been reported during the course of the clinical trials and/or from spontaneous sources:

- SOC Infections and infestations: pneumonia (not known)
- SOC Vascular disorders: lymphoedema (uncommon), thrombophlebitis (rare), deep vein thrombosis (uncommon), haematoma (rare)
- SOC Respiratory, thoracic and mediastinal disorders: pulmonary embolism (uncommon)
- SOC Skin and subcutaneous tissue disorders: scar pain (uncommon)
- SOC Musculoskeletal and connective tissue disorders: joint effusion (common), arthralgia (common), joint swelling (common), tendonitis (uncommon), muscular weakness (uncommon), patellofemoral pain syndrome (uncommon), osteonecrosis (rare), synovitis (uncommon), loose body in the joint (uncommon)
- SOC General disorders and administration site conditions: pain (common), gait disturbance (uncommon), discomfort (very rare)
- SOC Injury, poisoning and procedural complications: ligament sprain (uncommon), suture-related complication (rare), wound dehiscence (rare)

The recorded product- and surgery-related adverse reactions were in most cases not serious.

Paediatric population

In general, the adverse reactions in paediatric patients were similar in frequency and type to those seen in adult patients.

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 extraction 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 trial including 75 patients with focal cartilage defects (ICRS grade III or IV) in the knee with a defect size of 4-10 cm^2. 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 intention-to-treat (ITT) population consisted of 73 patients. The mean patient age was 34 years (range 19 to 48 years) with a mean body mass index (BMI) of 25.2. In all three dose groups a significant improvement ($\alpha < 0.05$) of the KOOS (Knee Injury and Osteoarthritis Outcome Score) after 12, 24, 36, 48 and 60 months compared to before treatment could be observed. For 'all dose groups' the mean overall KOOS increased in the first year after treatment from 57.0 ± 15.2 to 73.4 ± 17.3 on a scale from 0 (worst) to 100 (best) and continued to increase slightly, reaching 74.6 ± 17.6 after 18 months, 73.8 ± 18.4 after two years, 77.0 ± 17.8 after three years, 77.1 ± 18.6 after four years and 76.9 ± 19.3 at final follow-up after five 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, 36, 48 and 60 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 60 months from 59.8 at Visit 2 (3 months after treatment) up to 75.0 points in the group of patients treated with 3-7 spheroids/cm² defect, from 64.5 at Visit 2 up to 76.4 points in the dose group of 10-30 spheroids/cm² defect, and from 64.7 at Visit 2 up to 73.6 points in the dose group of 40-70 spheroids/cm² defect.

Furthermore, a multicentre, prospective, randomised, controlled Phase III clinical trial was conducted. The objective of the study was to compare the efficacy and safety of the treatment of cartilage defects (1 to less than 4 cm^2) at the femoral condyle of the knee joint with Spherox and microfracture treatment over a period of 5 years. Pivotal efficacy data were based on an interim analysis at 12 months after treatment. Additional statistical assessments were performed 24, 36, 48 and 60 months after treatment.

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 cm^2. ICRS grades were mostly IV A, followed by IIIB and IIIA (56, 22 and 10 patients respectively). None of the patients had received prior treatment with microfracture for their lesion less than one year before screening.
The assessment of the 'overall KOOS' for the ITT population showed that both treatments yielded a statistically significant improvement relative to baseline (day before arthroscopy). For the patients treated with Spherox the mean overall KOOS (scale of 0-100 ± SD) increased from 56.6 ± 15.4 at baseline to 81.5 ± 17.3 at 24 months after treatment. For patients treated by microfracture the mean overall KOOS increased from 51.7 ± 16.5 to 72.6 ± 19.5 after 24 months ($p < 0.0001$ for both treatment groups). With regard to the between-group analysis, the treatment with Spherox passed the test of non-inferiority compared with microfracture (Δ of 6.1 with lower bound of CI equal to –0.4 at the 24 months assessment).
The results at later time points were consistent with these findings. At 60 months follow-up, overall KOOS was 84.5 ± 16.1 after treatment with Spherox as compared to 75.4 ± 19.6 after microfracture. The total MOCART scores 3, 12, 18, 24 until 60 months after treatment did not differ significantly between the two treatment groups.
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.

Paediatric population

Spherox has been analysed in a non-interventional, open-label, multicentre surveillance study in 60 adolescent patients with closed epiphysial growth plates, aged 15 to < 18 years with focal cartilage defects (ICRS grade 3 or 4) in the knee with a defect size of 0.75 – 12.00 cm^2. The mean patient age was 16.5 years (range 15 to 17 years) with a mean body mass index (BMI) of 23.9. Mean (SD) follow-up time, defined as the interval between the date of implantation and date of the follow-up visit as documented by the physician was 48.4 (19.5) months. The mean (SD) overall KOOS score in the paediatric population at follow-up was 75.5 (18.2). MRI results according to the MOCART scoring system (0 = worst result; 100 = best result) at follow-up was mean (SD) 74.9 (18.5) and ranged from a minimum of 30 to a maximum of 100.

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 pouch. 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 pouch. 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/cm^2).

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

Precautions to be taken before handling or administering the medicinal product:

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.

Unused medicinal product and all material that has been in contact with Spherox (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

7. MARKETING AUTHORISATION HOLDER

CO.DON GmbH
Deutscher Platz 5d
04103 Leipzig
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: 10th July 2017
Date of latest renewal: 29th April 2022

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 AUTHORISATION

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 GmbH
Warthestraße 21
14513 Teltow
GERMANY

CO.DON GmbH
Deutscher Platz 5d
04103 Leipzig
GERMANY

Name and address of the manufacturer responsible for batch release

CO.DON GmbH
Warthestraße 21
14513 Teltow
GERMANY

CO.DON GmbH
Deutscher Platz 5d
04103 Leipzig
GERMANY

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (PSURs)**

The requirements for submission of PSURs 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.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (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 and use 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 educational programme is aimed at providing training to surgeons and other healthcare professionals (HCPs) on proper procurement, storage and handling of tissue and blood samples and application of Spherox.

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

- The Summary of Product Characteristics (SmPC) for Spherox
- Training material for surgeons and other healthcare professionals
- Prescriber checklist

- **The training material for surgeons and other healthcare professionals (HCPs)** shall contain the following key elements:
    - Information on Spherox, including the approved indication according to the SmPC
    - Detailed description of the biopsy procedure and blood collection, including the need to test for hepatitis B, hepatitis C, HIV and syphilis
    - Detailed description of application of Spherox
    - Patient's preparation for the procedure and subsequent monitoring, including recommendations on a rehabilitation programme post biopsy and implantation
    - Instructions on how to handle adverse events or reactions that might occur during/after biopsy and/or implantation
    - The need to officially confirm that the training has been conducted prior to the (first) biopsy procedure.
    - The importance to complete the prescriber checklist

- **The Prescriber checklist** shall contain the following key elements:
    - Corroboration that the patient receiving the medicinal product is the right patient receiving the right medicinal product in the approved indication according to the SmPC
    - Instructions on patient's eligibility including the need for screening and testing for hepatitis C, hepatitis B, HIV and syphilis

- Confirmation of the appropriate side of the implantation
- A specific reference to the fact that the patient has been informed and understands the benefits and risks of the medicinal product and the associated procedures
- Instructions on how to handle adverse events or reactions that might occur during/after biopsy and/or implantation

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 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 qualified and specialised surgeon trained in the ACI procedure of Spherox and is therefore restricted to appropriately specialised healthcare facilities
- Measures to ensure the traceability of the product and guarantee the identification of the patient and the product at each step.

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/cm^2 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/cm^2).

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

This medicine contains human cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CO.DON GmbH, Deutscher Platz 5d, 04103 Leipzig, Germany
Tel: +49 341 99190 200, Fax: +49 341 99190 309, 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 FOR APPLICATION SYSTEM CO.FIX 150 MM OR SYRINGE

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

Spherox 10–70 spheroids/cm^2 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 PACKAGINGUNITS

APPLICATION SYSTEM CO.FIX 150 MM OR SYRINGE

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

Application system co.fix 150 mm:
Spherox 10–70 spheroids/cm^2 implantation suspension

Syringe:
Spherox 10–70 spheroids/cm^2 implantation suspension

2. METHOD OF ADMINISTRATION

For intraarticular use

3. EXPIRY DATE

Application system co.fix 150 mm:
EXP {DD month YYYY} at {hours} CET

Syringe:
EXP {DD month YYYY} at {hours} CET

4. BATCH NUMBER, DONATION AND PRODUCT CODES

{Batch Number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

{Number of spheroids} sph

6. OTHER

For autologous use only.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Spherox 10-70 spheroids/cm^2 implantation suspension
spheroids of human autologous matrix-associated chondrocytes

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 is a medicine used to **repair damage to the cartilage of the knee** in adults and in adolescents whose bones in the joint have finished growing. Cartilage is a hard smooth layer inside your joints, on the ends of the bones. It protects the bones and allows joints to work smoothly. Spherox is used in adults, or adolescents whose bones have finished growing, when the cartilage in the knee joint is damaged, for example by acute injury, such as a fall or long-term wear due to incorrect weight bearing on the joint. Spherox is used to treat defects up to 10 cm² in size.

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. To make the spheroids, a small cartilage sample is taken from one of your joints during a minor operation, and then grown in the laboratory to make the medicine. The spheroids are implanted by surgery to the damaged cartilage area and stick to the damaged part. They are then expected to repair the damage with healthy and functional cartilage over time.

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

Do not use Spherox if

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

After the treatment, bleeding into the knee joint and possibly into the surrounding area may happen, mainly if you have an increased tendency of bleeding or if bleeding during the treatment could not be fully stopped. The physician will check in advance the risk that you may face a bleeding after the treatment. In that case, you will get medicine to decrease the risk of bleeding after the treatment.

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 **shall not be used** in children or adolescents whose bones in the knee joint have not finished growing.

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 to implant this medicine 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.

Treatment with Spherox is a two-step procedure:

Visit 1:
Evaluation of the damage to the cartilage, sample and blood taking

On the first visit, the doctor will examine the damage to your knee cartilage 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 will take a small **cartilage sample from your joint**. Most likely this will be from the same knee joint that has to be treated. 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 damaged area of cartilage in the knee during a second operation. This may also be carried out by keyhole surgery.

Rehabilitation

In order to allow your knee 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 follow 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 extent of the damage to the cartilage. Depending on the condition of the treated knee 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. The recorded side effects, either caused by the medicine or the surgery, were in most cases not serious.

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

- hypersensitivity (allergy) (one or more of the following symptoms may occur: skin redness, swelling in the treated area, low blood pressure, difficulties to breathe, swollen tongue or throat, weak and rapid pulse, sickness, vomiting, diarrhoea, dizziness, fainting, fever)
- blood clot in a vein (one or more of the following symptoms may occur: swelling in the leg, pain, increased warmth in the leg)

Other side effects

Side effects can occur with the following frequencies:
Common: may affect up to 1 in 10 people
- accumulation of fluid in the knee
- pain in the knee
- swelling in the knee
- accumulation of excess fluid in the bone marrow
- pain

Uncommon: may affect up to 1 in 100 people
- increase in size of the cartilage cells, softening of cartilage. ***You may notice symptoms, for example swelling or pain of the tissues around the knee.***
- cracking sounds in the knee
- joint lock in the knee
- impairment of walking
- tissue lump that may occur in the knee, fragment of cartilage or bone that freely floats in the knee joint space. ***You may notice symptoms, for example a painless heavy swelling of the treated knee, sudden pain or problems to move the treated knee.***
- cartilage cells in Spherox do not survive and grow
- any damage of knee cartilage

- ligament disorder
- tendon inflammation
- muscle weakness
- pain in the front of the knee or kneecap
- swelling of the treated leg due to obstructed flow of tissue fluid via the lymph vessels
- scar tissue pain
- blockage of a blood vessel in the lung
- inflammation of the inner layer of the joint capsule

Rare: may affect up to 1 in 1000 people
- disorder of bone formation, death of bone tissue, bone formation outside the skeleton. ***You may notice symptoms, for example swelling or pain of the tissues around the knee.***
- infection at the site of implantation
- inflammation of the knee joint caused by bacteria or fungi
- partial or complete detachment of the tissue beneath the bone and surrounding cartilage
- inflammation of the bone marrow caused by bacteria or fungi
- inflammation of the skin and/or the soft tissue caused by bacteria or fungi
- pain below the kneecap due to inflammation of the soft tissue
- 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)
- healing complication in the area of treatment
- reopening of a closed wound
- bruising

Very rare: may affect up to 1 in 10.000 people
- discomfort

Not known: frequency cannot be determined
- excessive scar tissue formation within the knee joint and/or surrounding of soft tissues
- infection of the lungs

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

This product will be carefully stored by medical staff in the hospital where the medicine will be given to you, and the storage instruction for them are as follow:

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 cm^2 of the cartilage defect.
- The other ingredient is sodium chloride used as transport solution.

What Spherox looks like and contents of the pack

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 that is a catheter (narrow tube) with a stem length of 150 mm.
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.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.