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/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.

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.

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, 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

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 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 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

The surgical procedure will have a major influence on the ability to drive and use machines. Also, during the rehabilitation period, the ability to drive and use machines may 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

Information on adverse reactions in from clinical trials 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	Joint noise, Joint lock, Synovial cyst
	Rare	Chondromalacia, Osteochondrosis, Osteonecrosis, Osteophyte formation, Arthritis infective
	Not known	Arthrofibrosis
General disorders and administration site conditions	Uncommon	Pain, Gait disturbance
Injury, poisoning and procedural complications	Rare	Hypertrophy, Graft delamination

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 to renege on the rehabilitation protocol.

Hypertrophy of the transplant
A symptomatic hypertrophy of the transplant 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 disorder: 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)
- SOC General disorders and administration site conditions: pain (uncommon), gait disturbance (uncommon), discomfort (very rare)
- SOC Injury, poisoning and procedural complications: ligament sprain (uncommon), suture-related complication (rare), wound dehiscence (rare)

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 Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

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 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 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 and 36 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, 23 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 78.7 ± 18.6 at the follow-up visit 12 months after treatment, improved up to the 24 months visit to 81.5 ± 17.3, reached 83.2 ± 14.9 at the 36 months visit and 84.4 ± 15.8 at the 48 months visit. For patients treated by microfracture the mean overall KOOS increased from 51.7 ± 16.5 to 68.1 ± 18.6 after 12 months, 72.6 ± 19.5 after 24 months and 76.3 ± 17.1 after 36 months and 76.5 ± 18.2 after 48 months ($p < 0.0001$ in all cases 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 5.7 with lower bound of CI equal to –1.0 at the 12 months assessment, Δ of 6.1 with lower bound of CI equal to –0.4 at the 24 months assessment, Δ 4.5 with lower bound of CI equal to -1.3 at 36 months assessment, and Δ of 5.5 with lower bound of CI equal to -0.7 at the 48 months assessment). The total MOCART scores 3, 12, 18, 24, 36 and 48 months after treatment did not differ substantially 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.

Further follow-up assessments of up to 5 years will be performed to generate long-term efficacy data on the treatment with Spherox.

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).

<u>Pack sizes</u>

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

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
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th July 2017

10. DATE OF REVISION OF THE TEXT

09/2020

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