Summary of Risk Management Plan (RMP) for Spherox (spheroids of human autologous matrix-associated chondrocytes for implantation)

Document Version: 1.0
Document Date: 26.04.2019
Based on EU-RMP Version 5.0 (25.07.2017)
CO.DON Schweiz GmbH
The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Spherox is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the ‘Arzneimittelinformation’ approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Spherox in Switzerland is the ‘Arzneimittelinformation’ (see www.swissmedic.ch) approved and authorised by Swissmedic.

CO.DON Schweiz GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Spherox.
Summary of Risk Management Plan for Spherox

This is a summary of the Risk Management Plan (RMP) for Spherox. The RMP details important risks of Spherox, how these risks can be minimised, and how more information will be obtained about Spherox risks and uncertainties (missing information).

Spherox's summary of product characteristics (‘Schweizer Fachinformation’) and its package leaflet (‘Schweizer Patienteninformation’) give essential information to healthcare professionals and patients on how Spherox should be used.

Important new concerns or changes to the current ones will be included in updates of the RMP for Spherox.

I. The medicine and what it is used for

Spherox is authorised for repairing symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (ICRS grade III or IV) with defect sizes from 2 to 10 cm² in adults that responded inadequately to conservative (non-operative) treatments. It contains spheroids of human autologous matrix-associated chondrocytes as the active substance and it is given by implantation into the knee joint.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Spherox, together with measures to minimise such risks and the proposed studies for learning more about Spherox's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the ‘Schweizer Patienteninformation’ and ‘Schweizer Fachinformation’ addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute **routine risk minimisation** measures.

In case of Spherox, these measures are supplemented with **additional risk minimisation measures** mentioned under relevant **important risks**, below.

In addition to these measures, information about adverse reactions is continuously collected and regularly analysed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute **routine pharmacovigilance activities**.

If important information that may affect the safe use of Spherox is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Spherox are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Spherox. Potential risks are concerns for which an association with the use of this medicinal product is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicinal product).
| Important identified risks | • Delamination of transplant  
• Hypertrophy of transplant  
• Lack of efficacy/treatment failure (result of graft delamination) |
|-----------------------------|-------------------------------------------------------------|
| Important potential risks   | • Medication error/maladministration  
• Local infection (due to surgical procedure)  
• Other surgery-related events  
• Interaction of the transplant with antibiotics or disinfectants  
• Transmission of infectious agent/disease |
| Missing information         | • Long-term safety and efficacy  
• Interacting substances used e.g. pain-relieving medication and corticosteroids |

**II.B Summary of important risks**

**Identified risks**

<table>
<thead>
<tr>
<th>Identified risk</th>
<th>(Partial or complete) Delamination of transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of linking the risk to the medicine</td>
<td>(Niemeyer, Pestka et al. 2008) classified four (4) major complications for the need of a re-surgery. These are (1) hypertrophy of the regenerated cartilage; (2) insufficient fusion of the regenerated cartilage and healthy cartilage at the edge of the former defect; (3) graft failure or formation of an insufficient regenerative cartilage and (4) delamination, which describes a shearing of the regenerative cartilage from the subchondral lamella in regularly formed cartilage tissue. In the remainder of patients, various MRI diagnoses in combination with clinical findings were made that led to the need for revision surgery (delamination and heterotopic ossifications found within the regenerative tissue). (Harris et al., 2011) identified 82 studies for inclusion (5276 subjects were analysed; 6080 defects) with 305 failures overall (5.8% subjects; mean time to failure 22 months). Re-operation rate after periosteal ACI (PACI), collagen-membrane cover ACI (CACI), and second-generation ACI was 36%, 40%, and 18%, respectively. Hypertrophy and delamination are most commonly seen after PACI. Arthrofibrosis is most commonly seen after arthrotomy-based ACI. Use of a collagen-membrane cover, second-generation techniques, and allarthroscopic, second-generation approaches have reduced the failure, complication, and re-operation rate after ACI.</td>
</tr>
</tbody>
</table>

**Risk factors and risk groups**

Patients with joint trauma or insufficient containment of the defect are supposed to have an increased risk.

**Risk minimisation activities**

*Routine risk minimisation measures:*  
Section 4 of the ‘Schweizer Fachinformation’-indication  
Section 5 of the ‘Schweizer Fachinformation’-administration  
Section 7 of the ‘Schweizer Fachinformation’-special warnings and precaution for use  
Section 11 of the ‘Schweizer Fachinformation’-side effects  

*Additional risk minimisation measures:*  
Educational/Training material for surgeons and other healthcare professionals
<table>
<thead>
<tr>
<th>Identified risk</th>
<th>Hypertrophy of transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of linking the risk to the medicine</td>
<td>The majority of complications after ACI treatment can be summarised as hypertrophy of the transplanted cartilage, malfusion, (partial) graft failure, and delamination. Among those, the overall complication rate and incidence of hypertrophy of the transplant were higher for periosteum-covered ACI. Furthermore, an increased rate of symptomatic hypertrophy was found for patellar defects (Niemeyer, Pestka et al. 2008). In the literature the most common problem after the classic ACI procedure is a periosteal hypertrophy described as being up to 36% (Gooding, Bartlett et al. 2006), (Driesang and Hunziker 2000), (Micheli, Browne et al. 2001), (Henderson, Flood et al. 2004) (Niethammer, Loitzsch et al. 2018).</td>
</tr>
<tr>
<td>Risk factors and risk groups</td>
<td>There are no known risk groups or specific risk factors for transplant hypertrophy in patients treated with Spherox. Patients may require debridement of the hypertrophic tissue via arthroscopy.</td>
</tr>
</tbody>
</table>
| Risk minimisation activities | **Routine risk minimisation measures:**  
Section 4 of the ‘Schweizer Fachinformation’-indication  
Section 5 of the ‘Schweizer Fachinformation’-administration  
Section 7 of the ‘Schweizer Fachinformation’-special warnings and precaution for use  
Section 11 of the ‘Schweizer Fachinformation’-side effects  
**Additional risk minimisation measures:**  
Educational/Training material for surgeons and other healthcare professionals |

<table>
<thead>
<tr>
<th>Identified risk</th>
<th>Lack of efficacy (result of delamination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of linking the risk to the medicine</td>
<td>Graft delamination or removal / loss, results in lack of implant efficacy and, thus, in transplant / treatment failure and as a consequence leading to a re-surgery. (Pestka J., et al., 2018) reported for about a total of 88 patients (3.3%) the need for revision surgery as early as 12 months postoperatively. The most common causes were arthrofibrosis and painful restriction of joint movement (1.0%), secondary meniscus abnormalities (0.4%), and additional cartilage lesions in the same knee joint but at another location (0.19%). Revision rates did not differ significantly among surgical techniques. (Niemeyer P., et al., 2008) classified four (4) major complications for the need of a re-surgery. These are (1) hypertrophy of the regenerated cartilage, which can be suggested if within the debrided defect area, a mechanically stable regenerate has formed that extends to the level of the native surrounding cartilage; (2) insufficient fusion of the regenerated cartilage and healthy cartilage at the edge of the former defect, which can be diagnosed if after ACI an intact and functionally stable regenerative tissue has formed but is not integrated entirely into the surrounding cartilage; (3) graft failure or formation of an insufficient regenerative cartilage and (4) delamination, which describes a shearing of the regenerative cartilage from the subchondral lamella in regularly formed cartilage tissue. Hypertrophy of the newly formed cartilage was observed in four (4) cases (7.7%). Osteochondral defects (necrosis of the subchondral bone) gave indication for revision surgery in 3 cases (5.8%). In 5 cases (9.6%), MRI showed an increasing subchondral edema. In the remainder of patients, various MRI diagnoses in combination with clinical findings were made that led to the need for revision surgery (delamination and heterotopic ossifications found within the regenerative tissue).</td>
</tr>
</tbody>
</table>
### Risk factors and risk groups
Patients with joint trauma or insufficient containment of the defect are supposed to have an increased risk.

#### Risk minimisation activities

- **Routine risk minimisation measures:**
  - Section 4 of the ‘Schweizer Fachinformation’-indication
  - Section 5 of the ‘Schweizer Fachinformation’-administration
  - Section 7 of the ‘Schweizer Fachinformation’-special warnings and precaution for use
  - Section 11 of the ‘Schweizer Fachinformation’-side effects

- **Additional risk minimisation measures:**
  - Educational/Training material for surgeons and other healthcare professionals

### Important potential risks

<table>
<thead>
<tr>
<th>Potential risk</th>
<th>Medication error/maladministration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence for linking the risk to the medicine</td>
<td>The treatment process with Spherox involves the following stages at which errors might occur:</td>
</tr>
<tr>
<td></td>
<td>• During tissue procurement and patients’ blood taking: Possible errors include, e.g. removal of mixed tissue (cartilage plus bone), incorrect packaging, labelling and storage</td>
</tr>
<tr>
<td></td>
<td>• During application of the medicinal product within the transplantation procedure: e.g. dose in correlation to defect size, etc.</td>
</tr>
<tr>
<td></td>
<td>• Incorrect administration technique, e.g. unsterile implantation</td>
</tr>
<tr>
<td></td>
<td>• Medication error at patient level, this could occur when a patient fails to follow treatment instructions (e.g. lack of adherence)</td>
</tr>
<tr>
<td></td>
<td>• Other factors, e.g. human factors, lack of experience by the treating surgeon</td>
</tr>
<tr>
<td>Risk factors and risk groups</td>
<td>The risk of medications error/maladministration increases if the proper handling of Spherox has not been trained adequately.</td>
</tr>
</tbody>
</table>

#### Risk minimisation activities

- **Routine risk minimisation measures:**
  - Section 4 of the ‘Schweizer Fachinformation’-indication
  - Section 5 of the ‘Schweizer Fachinformation’-administration
  - Section 7 of the ‘Schweizer Fachinformation’-special warnings and precaution for use

- **Additional risk minimisation measures:**
  - Educational/Training material for surgeons and other healthcare professionals
### Potential risk | Local infection (due to surgical procedure)
--- | ---
Evidence for linking the risk to the medicine | (Harris et al., 2011) reported superficial and deep infection as one complication after ACI resulting into transplant failure and need for re-surgery after ACI, for second generation ACI as of <1%, for third generation 0%. (Pestka et al., 2018) reported infection (n= 10) among the most common causes for a revision surgery.

### Risk factors and risk groups
Patients with osteoarthritis (contraindication for Spherox) or other inflammation process in the joint

### Risk minimisation activities
**Routine risk minimisation measures:**
- Section 4 of the ‘Schweizer Fachinformation’-indication
- Section 5 of the ‘Schweizer Fachinformation’-administration
- Section 6 of the ‘Schweizer Fachinformation’-contraindication
- Section 7 of the ‘Schweizer Fachinformation’-special warnings and precaution for use
- Section 11 of the ‘Schweizer Fachinformation’-side effects

**Additional risk minimisation measures:**
- Educational/Training material for surgeons and other healthcare professionals

### Potential risk | Other surgery related events (e.g. pain, joint effusion / swelling, thrombosis, embolism, bleeding, nerve injuries)
--- | ---
Evidence for linking the risk to the medicine | Not applicable

### Risk factors and risk groups
Related to the medical history / concomitant medication of the patient

### Risk minimisation activities
**Routine risk minimisation measures:**
- Section 4 of the ‘Schweizer Fachinformation’-indication
- Section 5 of the ‘Schweizer Fachinformation’-administration
- Section 7 of the ‘Schweizer Fachinformation’-special warnings and precaution for use
- Section 11 of the ‘Schweizer Fachinformation’-side effects

**Additional risk minimisation measures:**
- Educational/Training material for surgeons and other healthcare professionals

### Potential risk | Interaction of the transplant with antibiotics or disinfectants
--- | ---
Evidence for linking the risk to the medicine | The cartilage tissue is strongly related to its surrounding organic environment and particularly sensitive to small alterations in features such as oxygen saturation, heat and pH. Antibiotics are the most common additives used in irrigation solutions for open fractures including open joint fractures. However, few studies have investigated the toxic effects of antibiotics on articular cartilage. All these were in-vitro or short-term in-vivo studies without considering the potential recovery of chondrocytes. The purpose of this study was to evaluate the delayed effects of intra-articular injection of cefazolin, gentamicin and vancomycin on articular cartilage (Mah, Lee et al. 1991, Yang, Cheng et al. 1993, Gradinger, Trager et al. 1995, Lescun, Adams et al. 2002, Cheng, Jou et al. 2004, Anglen 2005, Chu, Szczodry et al. 2010, Akgun, Kocaoglu et al. 2014)
### Risk factors and risk groups

<table>
<thead>
<tr>
<th>People involved in the handling / procurement of Spherox</th>
</tr>
</thead>
</table>

### Risk minimisation activities

#### Routine risk minimisation measures:
- Section 4 of the ‘Schweizer Fachinformation’-indication
- Section 5 of the ‘Schweizer Fachinformation’-administration
- Section 7 of the ‘Schweizer Fachinformation’-special warnings and precaution for use
- Section 8 of the ‘Schweizer Fachinformation’-interactions

#### Additional risk minimisation measures:
- Educational/Training material for surgeons and other healthcare professionals

### Potential risk

#### Transmission of infectious agent/disease

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Not applicable</th>
</tr>
</thead>
</table>

#### Risk factors and risk groups

Spherox is intended solely for autologous use. Patients undergoing the surgical procedures associated with Spherox are not routinely tested for transmissible infectious diseases. Therefore, the cartilage biopsy and the Spherox may carry the risk of transmitting infectious diseases to the healthcare professional handling these tissues. Accordingly, healthcare professionals should employ universal precautions in handling the tissue samples and the Spherox.

#### Risk minimisation activities

##### Routine risk minimisation measures:
- Section 4 of the ‘Schweizer Fachinformation’-indication
- Section 5 of the ‘Schweizer Fachinformation’-administration
- Section 6 of the ‘Schweizer Fachinformation’-contraindication
- Section 7 of the ‘Schweizer Fachinformation’-special warnings and precaution for use
- Section 8 of the ‘Schweizer Fachinformation’-interactions

##### Additional risk minimisation measures:
- Educational/Training material for surgeons and other healthcare professionals

### Missing information

#### Missing Information

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>The safety and efficacy in long-term studies with Spherox has not been established yet.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>Patients exposed to Spherox in the approved indication.</td>
</tr>
</tbody>
</table>

#### Interaction with pain-relieving medication

Evidence of source and strength of evidence

Regarding accompanying pain-relieving medication, the application of local anesthesia needs to be avoided at all times. It has been described that this anesthesia displays toxic effects on cartilage tissue and therefore endangers the efficacy of the therapy. In contrast, the systemic application of painkillers does not indicate any problems. However, in the case of subchondral bone pathologies, the inhibitory effect of ibuprofen on bone healing should be taken into account and the treatment with non-steroidal anti-inflammatory drugs (antiphlogistics) for pain relieve should be avoided. In the case of cartilage defects that are treated with Spherox, on the other hand,
treatment with non-steroidal antiphlogistics as well as with weak and strong opioids seems to be uncomplicated. The perioperative pain relieve therapy is an extensively studied area of expertise as part of surgery and therefore, no complication is being expected. While using Spherox in routine clinical practice and in clinical trials, no adverse event reports that resulted from the use of pain medication in combination with the Spherox product have been reported (Beyzadeoglu, Torun Kose et al. 2012, Breu, Rosenmeier et al. 2013).

| Risk factors and risk groups | Patients being treated with Spherox thereby undergoing a two-step surgical procedure. |

<table>
<thead>
<tr>
<th>Missing Information</th>
<th>Interaction with corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of source and strength of evidence</td>
<td>Intraarticular injection of corticosteroids in combination with local anaesthesia are commonly used for management of pain and inflammatory symptoms after arthroscopic procedures or arthritic joint conditions. Evidence for cytotoxic effects of corticosteroids on cartilage is inconsistent as the majority of these studies have been performed on monolayer cell cultures that do not replicate the extracellular matrix and cell heterogeneity found in either intact tissue samples or in vivo. Therefore, it should be considered that there is a possible negative effect on viability of chondrocytes when contemplating intraarticular administration. refer to (Stueber, Karsten et al. 2014, Sherman, Khazai et al. 2015; Seth et al, 2015; Syed et al. 2011).</td>
</tr>
<tr>
<td>Risk factors and risk groups</td>
<td>Patients being treated with Spherox thereby undergoing a two-step surgical procedure.</td>
</tr>
</tbody>
</table>

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

**Study short name:** Post-authorisation efficacy study (PAES): 60-month follow-up data for clinical study cod 16 HS 13:

Purpose of the study is 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.

**Study short name:** Swiss post-marketing observational study: 60 months follow-up assessment.

Purpose of the study is to assess the short- and long-term efficacy and safety of Spherox in patients treated with cartilage defects of the knee with a defect size between 2 and 10 cm² in Switzerland.