Part VI: Summary of the risk management plan

Summary of risk management plan for Spherox (spheroids of human autologous matrix-associated chondrocytes)

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' summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Spherox should be used.

This summary of the RMP for Spherox should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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 defects to the cartilage in the knee who have symptoms such as pain and problems moving the knee (*see SmPC for the full indication*). It contains spheroids of human autologous matrix-associated chondrocytes as the active substance and it is given by implantation in the knee joint.

For EU: *Further information about the evaluation of Spherox' benefits can be found in Spherox' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/spherox.*

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' 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 PL and SmPC 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 collected continuously 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).

Summary of safety concerns	
Important identified risks	• Graft delamination • (Implant site/cartilage) hypertrophy • Lack of efficacy/treatment failure (e.g. result of graft delamination, graft removal/loss, graft rejection, transplant failure) • Implant site infection
Important potential risks	• Medication error/maladministration • Other surgery related events (e.g. arthralgia, joint effusion, joint swelling, thrombosis, embolism) • Interaction of the implant with antibiotics or disinfectants • Transmission of infectious agent/disease • Procedure related events (e.g. related to the procurement of raw material, transport and administration)
Missing information	• Interactions with e.g. pain-relieving medication and corticosteroids • Long-term safety and efficacy

II.B Summary of important risks

Important identified risk	**Graft delamination**
Evidence for linking the risk to the medicine	(Niemeyer et al., 2008a) 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. (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. Female gender, age over 40 years, increased weight, previous cartilage surgery, and meniscus loss showed increased risk for revision surgery or graft failures (Martincic et al., 2019). Also (Merkely et al., 2020) concluded from their study results (368 patients (209 ACI and 159 OCA)) that hypertension, defect size and female gender seem to predict ACI graft failure.
Risk factors and risk groups	Patients with joint trauma or insufficient containment of the defect are supposed to have an increased risk.
Risk minimisation measures	Routine risk minimisation measure: • SmPC Section 4.8. • PL Section 4 Additional risk minimisation measures: • Training material (incl. prescriber checklist) for surgeons and other HCPs.

Important identified risk	**(Implant site/cartilage) hypertrophy**
Evidence for linking the risk to the medicine	The majority of complications after ACI treatment can be summarised as hypertrophy of the implanted cartilage, malfusion, (partial) graft failure, and delamination. Among those, the overall complication rate and incidence of hypertrophy of the implant were higher for periosteum-covered ACI ((Gooding et al., 2006); (Driesang & Hunziker, 2000); (Micheli et al., 2001); (Henderson et al., 2004); (Ebert et al., 2017)). Graft hypertrophy after ACI was seen in 22% (n = 20) of the patients (Niethammer et al., 2018). Furthermore, an increased rate of symptomatic hypertrophy was found for patellar defects (Niemeyer et al., 2008b).
Risk factors and risk groups	Risk groups or specific risk factors for implant hypertrophy in patients treated with Spherox are unknown.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8. • PL Section 4. Additional risk minimisation measures: • Training material (incl. prescriber checklist) for surgeons and other HCPs.

Important identified risk	**Lack of efficacy/treatment failure (e.g. result of graft delamination, graft removal/loss, graft rejection, transplant failure)**
Evidence for linking the risk to the medicine	(Pestka 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 et al., 2008a) 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. Osteochondral defects (necrosis of the subchondral bone) gave indication for revision surgery in 3 cases (5.8%). (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. The primary reasons for chondroplasty were hypertrophy of the ACI graft (17; periosteum in 14, collagen membrane in 3), delamination of the ACI graft (5; periosteum in 4, collagen membrane in 1), and new chondral lesions (3) (Ogura et al., 2019). (Ackermann et al., 2020a) concluded from their results that failures of graft survivorship in patients (60) who underwent ACI for the treatment of focal full-thickness cartilage on the medial femoral condyle with and without concomitant high tibial osteotomy are significantly more often with valgus alignment. (p= 0.0002), whereas neutral mechanical alignment resulted in a significantly longer graft survival compared with slight valgus alignment (p = 0.003 and p = 0.05, respectively). (Calcei et al., 2021) concluded from their retrospective cohort study that concomitant osteotomy at the time of index ACI or OCA procedure significantly reduces the risk of reoperation with a similar rate of complications and similar overall costs compared with isolated ACI or OCA. They compared the (1) reoperation rates, (2) 30-day complication rates, and (3) cost differences between patients undergoing isolated ACI or osteochondral allograft transplantation (OCA) procedures alone versus patients with concomitant osteotomy. Patients with knee ACI or OCA with minimum 2-year follow-up were queried from a US national insurance database and divided into patients who underwent isolated cartilage restoration procedure and patients who underwent concomitant osteotomy. A total of 1,113 patients (402 ACI, 67 ACI + osteotomy, 552 OCA, 92 OCA + osteotomy) were found (mean follow-up of 39.0 months). Reoperation rate defined by ipsilateral knee procedure after the index surgery was significantly higher after isolated ACI or OCA compared to ACI or OCA plus concomitant osteotomy (ACI 68.7% vs. ACI + osteotomy 23.9%; OCA 34.8% vs. OCA + osteotomy 16.3%). Overall complication rates (assessed using ICD-9-CM codes) were similar between isolated ACI (3.0%) and ACI + osteotomy (4.5%) groups and OCA (2.5%) and OCA + osteotomy (3.3%) groups. Payments were significantly higher in the osteotomy groups at day of surgery and 9 months compared to isolated ACI or OCA, but costs were similar by 2 years postoperatively.
Risk factors and risk groups	Patients with joint trauma or insufficient containment of the defect are supposed to have an increased risk. Female gender, age over 40 years, increased weight, previous cartilage surgery, and meniscus loss showed increased risk for revision surgery or graft failures (Martincic et al., 2019).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, 4.3, 4.4 and 4.8 • PL Section 3 and 4 Additional risk minimisation measures: • Training material (incl. prescriber checklist) for surgeons and other HCPs.

Important identified risk	**Implant site infection**
Evidence for linking the risk to the medicine	Most surgical infections originate from bacteria that enter the wound at the time of operation. The causative pathogens originate from the patient's endogenous microflora, from the operating room environment, or from organisms shed by the operating room team (Cristina *et al*, 2016; Pittet & Ducel, 1994). Infection is a rare complication of knee arthroscopies of below 1% (Sircana *et al*, 2019). (Harris et al., 2011; Sircana *et al.*, 2019) reported superficial and deep infection as one complication after ACI resulting into transplant failure and need for re-surgery after ACI. (Pestka et al., 2018) reported infection (n= 10) among the most common causes for a revision surgery after cartilage regenerative surgery of the knee (including ACI and bone marrow stimulation).
Risk factors and risk groups	Patients with osteoarthritis (contraindication for Spherox) or other inflammation process in the joint.

Risk minimisation measures	Routine risk minimisation measures: • SmPC Section4.4 and 4.8 • PL Section 4 Additional risk minimisation measures: • Training material (incl. prescriber checklist) for surgeons and other HCPs.

Important potential risk	**Medication error/maladministration**
Evidence for linking the risk to the medicine	Not applicable.
Risk factors and risk groups	Incorrect handling/administration technique and/or lack of experience. Patients to whom Spherox is applied to.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 and 4.4 Additional risk minimisation measures: • Training material (incl. prescriber checklist) for surgeons and other HCPs.

Important potential risk	**Other surgery related events** (e.g. arthralgia joint effusion, joint swelling, thrombosis, embolism)
Evidence for linking the risk to the medicine	(Ebert et al., 2017) prospectively evaluated the first 31 patients (15 male, 16 female) who underwent MACI via arthroscopic surgery to address symptomatic tibiofemoral chondral lesions (medial femoral condyle (n = 5), lateral femoral condyle (n = 1), and lateral tibial plateau (n = 1). No early postoperative complications, such as wound infections, haematomas, or deep vein thrombosis (DVT), that may be observed more commonly in more invasive techniques were found. Adverse outcome after elective knee arthroscopies measures included pulmonary embolism (PE), deep vein thrombosis (DVT), haemarthrosis, effusion and synovitis, cellulitis, wound infection, synovial fistula, acute renal failure, myocardial infarct, stroke, and death. The most common adverse outcomes within 30 days were DVT (579, 0.32%), effusion and synovitis (154, 0.09%), PE (147, 0.08%), and hemarthrosis (134, 0.07%). Potential risk factors for complications were older age, presence of comorbidity (Bohensky et al., 2013).
Risk factors and risk groups	Risk factors are related to the medical history and/or concomitant medication of the patient.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • PL Section 4 Additional risk minimisation measures: • Training material (incl. prescriber checklist) for surgeons and other HCPs.

Important potential risk	**Interaction of the implant 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. Few studies have investigated the toxic effects of antibiotics on articular cartilage, all were *in vitro* or short-term *in vivo* studies without considering the potential recovery of chondrocytes ((Akgun et al., 2014, Anglen, 2005, Cheng et al., 2004, Chu et al., 2010, Gradinger et al., 1995, Lescun et al., 2002, Mah et al., 1991, Yang et al., 1993).
Risk factors and risk groups	Incorrect handling of disinfectants; administration of antibiotics during surgery. Patients being treated with antibiotics during surgery.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.5

	Additional risk minimisation measures: • Training material (incl. prescriber checklist) for surgeons and other HCPs.

Important potential risk	**Transmission of infectious agent/disease**
Evidence for linking the risk to the medicine	Infectious disease transmission through organ and tissue transplantation has been associated with severe complications in recipients (Greenwald *et al*, 2012). The transmission of donor-derived infections is relatively efficient with viable cells and tissue as well as blood (Fishman *et al*, 2012). Donor-derived infections are less relevant for Spherox treatment since donor and recipient are the same, but contamination during transport and cell cultivation has to be taken into account. Some studies consider preservation-fluid contamination including those occurring during the procurement process (Yahav & Manuel, 2019), but little is known about the incidences for this subgroup. HCPs can be infected by parenteral injection of blood, or through exposure of the skin or mucous membranes to blood or other body fluids. The nature and frequency of blood contact among surgical personnel have been studied prospectively. Between 6% and 50% of operations involved one or more blood contacts, and one or more sharp injuries were noted in from 1.3% to 15.4% of procedures. These varied with the type of surgery and, within each specialty, procedure-specific rates are available. Serological surveillance of several thousand HCPs has shown that the risk of HIV seroconversion after a single percutaneous exposure is of the order of 0.3%, much less than that reported for hepatitis at 10% for HCV and 30% for HBV (Lemaire & Masson, 2000).
Risk factors and risk groups	Spherox is solely intended for autologous use, the donor of the biopsy material is also the recipient of the finished medicinal product. Contamination with infectious agents might occur during tissue procurement, transport and cell cultivation. Patients undergoing Spherox treatment are tested for HIV I/II, HBV, HCV, and syphilis prior to the implantation procedure. The biopsy procedure and Spherox treatment may carry the risk of transmitting of infectious agents/disease to HCPs as well as to personnel at the manufacturing site handling these tissues and blood samples. Both HCPs and personnel at the manufacturing site undergo strict safety precautions in handling the biopsy material, blood samples and Spherox.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3 and 4.4. • PL Section 2 Additional risk minimisation measures: • Training material (incl. prescriber checklist) for surgeons and other HCPs.

Important potential risk	**Procedure related events** (e.g. related to the procurement of raw material, transport, and administration)
Evidence for linking the risk to the medicine	The initial cartilage biopsy and the harvest of autologous chondrocytes are key steps at the beginning of every ACI procedure. These steps remain independent from different ACI techniques. The biopsy needs to assure that sufficient amounts of vital cartilage tissue can be collected without extensive donor side le morbidity. A standardized procedure will reliably and safely allow the extraction of sufficient quantities of cartilage samples. Standardized biopsies simplify chondrocyte isolation and cell expansion and guarantee safety and consistent quality (Niemeyer et al., 2010). Some trans-arthroscopic graft positioning is difficult to perform with a constant flow of saline and the inflow sometimes needs to be reduced or stopped. The disadvantage is that the joint capsule may then collapse and the sight for implantation will be reduced (Brittberg, 2019). Defect aetiology and quality of the cells are decisive for the clinical outcome (Pietschmann et al., 2009). Cell quality seems to be one of many factors that influences clinical outcome after ACI in patients with cartilage defects of the knee joint (Niemeyer et al., 2012).

Risk factors and risk groups	Risk factors related to the procedure (e.g. procurement of raw material, storage, transport and administration of the finished medicinal product) have an impact on the biological activity of the ATMP and, thus, might lead to lack of efficacy and as a consequence to transplant failure.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, 4.3, 4.4 and 4.5 Additional risk minimisation measures: • Training material (incl. prescriber checklist) for surgeons and other HCPs.

Missing information	**Interactions with e.g. pain-relieving medication and corticosteroids**
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.5 Additional risk minimisation measures: • Training material (incl. prescriber checklist) for surgeons and other HCPs.

Missing information	**Long-term safety and efficacy**
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 5.1 Additional risk minimisation measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • cod 16 HS 18 (Post-marketing observational study (Switzerland)) See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

In EU and UK no studies, which are conditions of the marketing authorisation are proposed or ongoing.

The following study is requested by Swissmedic:

Study short name: cod 16 HS 18 (post-marketing observational study)

Purpose of the study: The purpose of this prospective, open-label, non-interventional study is to confirm the safety and efficacy of the ATMP Spherox after application to patients in Switzerland for up to 5 years after treatment.

II.C.2 Other studies in post-authorisation development plan

None.