Summary of Safety and Clinical Performance

of

Suspension of Degradable Starch Microspheres

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device. The SSCP is not intended to replace the Instructions For Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The following information is intended for users/healthcare professionals.

Table of Content

1 Device identification and general information

Device trade names

The trade name of the medical device Suspension of Degradable Starch Microspheres (DSM) is EmboLog® S.

1.1 Manufacturer's name and address

Serumwerk Bernburg AG
Hallesche Landstraße 105 b
06406 Bernburg
Germany

1.2 Manufacturer's single registration number of the manufacturer

Single Registration Number (SRN): DE-MF-000005169

1.3 Basic Unique Device Identification-DI

Basic Unique Device Identification (Basic UDI-DI): 426020097DSMC3

1.4 Medical device nomenclature description/text

Nomenclature code (EMDN): C010402020303 EMBOLISATION PARTICLES AND MICROSPHERES

1.5 Class of device

Classification according to Annex VIII of Regulation (EU) 2017/745: Class III, Rule 7 (short-term surgically invasive devices)

1.6 Year when the first certificate (CE) was issued covering the device

The production of the degradable starch microspheres was established by Serumwerk Bernburg AG and its first certificate was issued in 2004 for the medical device EmboCept*. The microspheres were optimized in 2010 regarding degradation, which was distributed under the product name EmboCept®* S, latter being identical to EmboLog® S.

* trademark of PharmaCept GmbH

1.7 Authorised representative

Not applicable.

1.8 Notified Body

mdc medical device certification GmbH
Kriegerstraße 6
70191 Stuttgart
notified body number: 0483

2 Intended purpose, any indications, contraindications

2.1 Intended Purpose

EmboLog® S is intended for embolization of blood vessels, especially for the local application in minimal invasive treatment, such as intra-arterial occlusion in liver tumour therapy.

2.2 Indication and intended patients groups

EmboLog® S is intended for embolization of blood vessels, especially for the local application in minimal invasive treatment, such as intra-arterial occlusion in liver tumour therapy.
The device is administered by trained health care professionals.

2.3 Contraindication

Contraindications DSM

- Do not use if there are vascular anomalies in the target organ, if the artery is occluded, in the case of portal vein thrombosis, portal hypertension, portal vein invasion and severe liver impairment.
- Do not use for the diagnosis, management or correction of a defect in the heart or the central circulatory system.
  "Central circulatory system" means the following vessels:
  ascending aorta, coronary arteries, common carotid artery, external carotid artery, internal carotid artery, cerebral arteries, brachiocephalic trunk, veins of the heart, pulmonary veins, superior vena cava, inferior vena cava, aortic arch, descending aorta as far as bifurcation of the aorta.
- Do not use in case of blood values of serum albumin ≤2mg/dl serum creatinine ≥2 mg/dl.

Contraindication/Adverse events of cytostatic agents/contrast agents (e.g. Lipiodol)
Please refer to the contraindications/adverse events described in the package insert!

3 Device description

3.1 Description of the device

The medical device is a suspension of Degradable Starch Microspheres (DSM) in isotonic saline solution. DSM is a complex polymeric matrix, which is composed of partially hydrolyzed starch crosslinked via glycerol ether groups. DSM is non-immunogenic. Due to the swelling in water the particles have gel-like properties and which makes them flexible to be deformed within the vascular system.
Degradable Starch Microspheres can cause a temporary vascular occlusion until they are degraded by serum alpha-amylase. In-vivo the particles are degraded into oligomeric fragments by serum alpha-amylase and subsequently further digested. Fragments with low molecular weight are excreted by renal filtration (Artursson et al. 1989). Intravenous or intra-arterial injection of microspheres ranging in size from 0.1-5.0 µm are rapidly cleared from the blood stream by macrophages (Poste and Kirsh 1983). The degradation rate of starch microspheres depends on the endogenous amylase activity and on the properties of the spheres. The half-life in vitro at 37 °C is approximately 30-40 minutes. Thus, the product induces a transient vascular occlusion with a blood flow reduction in patients with HCC lesions for up to 90 minutes (Wiggermann et al. 2013). Consequently, treatment sessions using DSM-induced vascular

occlusion can be repeated. The short duration of the occlusion minimizes the risk of regional adverse effects.

The mode of action in intra-arterial chemo-occlusion is based on the following:

- Transient vascular occlusion in peritumoral blood vessels,
- Blood flow reduction after intra-arterial injection of the medical device has been shown in animals and patients,
- Increased duration of exposure of the cytostatic drug at the target area (e.g. prevention of rapid leaching in the hepatic parenchyma as a result of supply from the portal vein),
- Decreased systemic drug concentrations and thereby significant reducing of systemic side effects.

Constituents and Miscellaneous

Qualitative composition:

Amilomer/DSM (Degradable Starch Microspheres), sodium chloride, water for injection, sodium hydroxide

Quantitative information to the main active ingredient:

450 mg Amilomer in 7.5 ml isotonic saline solution
240 mg Amilomer in 4.0 ml isotonic saline solution

Declaration on particular substances:

The medical device DSM is not manufactured utilizing tissues or cells of human/animal origin or their derivates and does not contain a substance, which may be considered to be a medicinal product within the meaning point 2 Article 1 of of Directive 2001/83/EC.

Miscellaneous:

EmboLog® S must not be used after the expiry date! EmboLog® S contains no preservatives. Therefore, partially empty bottles must not be stored for later use.
The medical device is intended solely for single use and is not suitable for reprocessing.
For the safe use of EmboLog® S the administration has to be done by trained health care professionals.

Keep out of the reach and sight of children!
Prescription only

3.2 Previous generation and its differences

The production of degradable starch microspheres has been established at Serumwerk Bernburg AG since 2004. The developed and manufactured device, distributed by our former, exclusive distribution partner under its trademark EmboCept®*, was characterized by homogeneous, spherical particles that did not show any relevant deformations during catheter passage (Paprottka et al. 2016). The microspheres were optimized regarding degradation time (Wiggermann et al. 2013). To improve the safety and tolerability of the microspheres the half-life was reduced to about 30-40 minutes (*in-vitro*). The diameter of the starch

microspheres was not changed. The developed, manufactured and clinically proven starch microspheres are now distributed under the new product name **EmboLog® S** directly from Serumwerk Bernburg AG.

* registered trade name of PharmaCept GmbH

3.3 Description of any accessories

EmboLog® S is not provided with accessories.

3.4 Description of any other devices and products

The embolization effect of EmboLog® S leads to a short-term vascular occlusion of blood vessels and reduced blood flow.

When cytostatic drugs are administered prior to the intended embolization, the effect of EmboLog® S leads to an increased duration of exposure of the cytostatic drug at the target area. The following table show the most used cytostatic drugs.

Table 1: Substances often used in transarterial chemotherapy [Huppert et al. 2019]

Cytostatic agent	Maximum dose
Carboplatin	300 mg/m^2 BSA
Cisplatin	100 mg/m^2 BSA
Doxorubicin	50 mg/m^2 BSA
Epirubicin	75 mg/m^2 BSA
5-Fluorouracil	100 mg/m^2 BSA
Gemcitabine	1000 mg/m^2 BSA
Irinotecan	200 mg/m^2 BSA
Mitomycin C	10 mg/m^2 BSA
Oxaliplatin	660–680 mg/m^2 BSA

For information regarding to the choice of cytostatic agents, please contact embolog@serumwerk.de or refer to the following references:

- Lucatelli P, Burrel M, Guiu B, de Rubeis G, van Delden O, Helmberger T. CIRSE Standards of Practice on Hepatic Transarterial Chemoembolisation. Cardiovasc Intervent Radiol. 2021 Dec;44(12):1851-1867. doi: 10.1007/s00270-021-02968-1. Epub 2021 Oct 25. PMID: 34694454.

- Huppert P, Paprottka P, Albrecht T. Transarterielle Tumortherapie. In: Mahnken A, Thomas C, Wilhelm K, Hrsg. Interventionelle Radiologie. 1. Auflage. Stuttgart: Thieme; 2019.

4 Risks and warnings

4.1 Residual risks and undesirable effects

There are potential complications:

- Pains in the region of the target organ caused by vessel occlusion (usually subsides after about 30 – 60 minutes and disappears after approx. 1 hour),
- Ischaemic pain (epigastric discomfort, chest pains),
- Transient functional impairment in the target organ (e.g. elevated liver enzymes),

- Dyspnoea,
- Nausea, vomiting, diarrhoea, mucosal inflammation, fever, shivers, ulcers in the upper gastrointestinal tract can be caused by cytostatic drugs when given in timely relation to embolization

4.2 Warnings and precautions

The suspension must be shaken before any application and several times during administration because the starch microspheres tend to rapid sedimentation. In case of prior administration of cytostatic agent, the subsequent injection of EmboLog® S must be performed slowly. It is advisable to perform a check angiography at about 5 to 10-minute intervals to rule out any back-flow. **As soon as any back-flow starts, administration of the rest of the embolic agent must be stopped immediately.** Due to the short half-life of the embolizate (approx. 30 – 40 min**.)**, it may be assumed that resumption of blood flow will be observed after about 10 – 15 minutes' waiting time and the rest of the material can then be administered.
EmboLog® S must not be used after the expiry date! EmboLog® S contains no preservatives. Therefore, partially empty bottles must not be stored for later use.

4.3 Other relevant aspects of safety

Since introduction on the market

- No serious incidents were reported.
- No recalls were performed.
- No field safety corrective action was performed

In January 2016, a customer information letter was send out in order to inform on the indication of the medical device.

5 Summary of clinical evaluation and post-market clinical follow-up (PMCF)

5.1 Summary of clinical data related to equivalence device

In total, the clinical evaluation report based on Regulation (EU) 2017/745. Furthermore, the guideline MEDDEV 2.7/1 revision 4 and the guidance documents MDCG 2020-05 (Guidance on clinical evaluation – Equivalence) were used.
The clinical evaluation based on clinical data of equivalent products, namely degradable starch microspheres:

- EmboCept®*: Manufacturer Serumwerk Bernburg AG
- EmboCept®* S (identical to EmboLog® S): Manufacturer Serumwerk Bernburg AG
- Spherex: Manufacturer Kabi Pharmacia

All technical, biological and clinical characteristics are evaluated. The differences are minor and not expected to affect the clinical performance and clinical safety. All products are starch microspheres that are composed of partially hydrolyzed and cross-linked by glycerine-ether components. The particles are spherical and degradable. The intended purpose is the embolization of blood vessels, especially for the local application in a minimal invasive treatment, such as intra-arterial occlusion in liver tumour therapy.

The embolization effect leads to a short-term vascular occlusion of blood vessels and reduced blood flow. The systemic toxicity is significantly reduced compared to chemotherapy.

* registered trade name of PharmaCept GmbH

5.2 Summary of clinical data from conducted investigations of the device before the CE-marking

Not applicable.

5.3 Summary of clinical data from other sources

A comprehensive literature review was performed to gather clinical and safety data in support of CE-marking and to assist in documenting conformity with the relevant European MDR concerning device safety and performance.

5.3.1 Summary of clinical data on efficacy

Literature search strategies were designed to identify articles relevant to the EmboLog® S and comparable devices. The results of the literature review also provide verification that all clinical hazards have been addressed in the subject device risk analyses. Both favourable and unfavourable references have been identified and summarized.

Following main conclusions regarding the clinical performance of DSM based on literature data were drawn:

Table 2 Overview of main conclusions on efficacy

Conclusion	Reference
DSM-TACE significantly improves the efficacy and survival of the patients compared to cTACE (disease control DSM: 78% versus disease control lipiodol 38%). The main advantage is the short-term vessel occlusion, which reduces VEGF induction and risk of postembolization syndrome as compared to lipiodol	Vogl et al. 2020
Different cytostatics can be used, whether alone or in combinations. However, it must be ensured that there are no allergies to cytostatics.	Lucatelli P et al. 2021 Huppert P et al. 2019 Refer to also to Table 3
The combination with further therapy methods (e.g. Laser induced thermotherapy) is a feasible palliative treatment option	Zangos et al. 2001 Vogl et al. 2012 Vogl et al. 2010
DSM-TACE is effective with a disease control (DC) of 92 % and safe in intermediate-stage HCC, achieving an interesting downstaging rate for liver transplantation	Minici et al. 2021
DSM induces a transient vascular occlusion with a blood flow reduction in patients with HCC lesions for up to 90 minutes	Wiggermann et al. 2013
DSM-TACE allows the temporary occlusion of the smaller arterial vessels, improving overall therapeutic effectiveness by reducing the immediate wash-out of the cytostatic agent	Iezzi et al. 2018
A repetition of TACE-treatments can improve the efficacy and therefore the overall survival	Orlacchio et al. 2018 Massmann et al. 2015

A disease control (DC) of 100 % is reported in with doxorubicin alone	Orlacchio et al. 2015
A combination of cytostatic drug showed improvements in median survival time (OS) (Mitomycin C: OS 6 month versus Mitomycin C, Gemcitabine, Cisplatin: OS 15.3 month for	Vogl et al. 2013
Chemoocclusion with DSM did not improve response or survival significantly compared to transarterial chemoperfusion in advanced non-resectable hepatocellular carcinoma.	Kirchhoff et al. 2006
BCLC C and D stage patients did not benefit substantially from DSM-TACE in terms of overall survival although their hepatic tumour responses were promising. Their prognosis seems to be influenced mainly by other liver function.	Gross et al. 2020

In total, the important clinical benefit for the use of the medical device is to improve the tumour response and a prolonged survival in liver tumour therapy. Transarterial Chemoembolization (TACE) is a minimal-invasive image-guided transarterial catheter-directed therapy, which has been used especially for the treatment of liver tumours. The embolization effect of DSM leads to a short-term vascular occlusion of blood vessels and reduced blood flow. When cytostatic drugs are administered prior to the intended embolization, the effect of DSM leads to an increased duration of exposure of the cytostatic drug at the target area. A repeated TACE procedure is reported to improve the tumour response.

5.3.2 Summary of clinical data on safety

Numerous literature references have been assessed regarding the safety of EmboLog® S and comparable products. Often, transient PES related events such as abdominal pain, fever, nausea and vomiting are described as frequent adverse events. The aforementioned adverse events are described as transient and easily solved with standard analgesic or antiemetic medication during interventions. Since most of the conducted investigations are performed in combination with one or more cytostatic agents, a clear allocation whether an adverse event is related to EmboLog® S or to the concomitant administered drug is difficult. The summary of product characteristics of the administered drug should be consulted concerning possible adverse events.

Table 3 Overview of conclusions on safety

Reference	Cytostatics	Reported AEs/Conclusions if available
Kirchhoff et al. 2006	Cisplatin Doxorubicin	PES related symptoms Upper gastro-intestinal bleeding Cholecystitis AEs likely related to cytostatic: Thrombocytopenia Leukopenia Hair loss Conclusion: In summary, the present trial indicates that transient chemoocclusion using DSM did not solve the dilemma of increasing anti-tumour efficiency without increasing toxicity and side-effects. Further large trials on embolizing agents are needed to better identify those patients that will profit from regional therapy in terms of survival at an acceptable rate of side-effects.
Taguchi et al. 1992	Mitomycin C Doxorubicin	PES related symptoms Two deaths of patients occurred during this study. One case could be attributed to a high dose of mitomycin C. In the other case a relationship to mitomycin C and DSM could not be refuted. Conclusion: The risk of serious adverse events seems not to be unreasonable provided that adequate precautionary measures are taken.
Czejka et al. 1991	Mitomycin C	PES related symptoms Conclusion: Methods cause a distinctly accelerated diffusion of mitomycin into the tissue of the tumour region by change of the hemodynamics, leading to lowered systemic side-effects.
Vogl et al. 2006	Gemcitabine	significant increase in pain and took more analgesics for at least 4 week increase and decrease in weight Conclusion: In chemoembolization an increased dosage can be tolerated as compared to local chemoperfusion.
Orlacchio et al. 2019	Doxorubicin	PES related symptoms Nonsurgical cholecystitis Hepatic abscesses Portal vein thrombosis followed by gastroesophageal variceal bleeding, One death (due to massive hepatic artery occlusion and liver failure; procedure-related) Conclusion: DSMs-TACE is a safe and effective therapy for patients with HCC
Lindgaard et al. 2019	Oxaliplatin Capecitabine	PES-related symptoms AEs likely related to cytostatic: Hand-foot syndrome Neuropathy Conclusion: HAT oxaliplatin in combination with capecitabine is safe and efficient in patients with MBC

Reference	Cytostatics	Reported AEs/Conclusions if available
Schicho et al. 2017-1	Doxorubicin Epirubicin Carboplatin	PES-related symptoms Dyspnoea Shivering Allergic reaction Conclusion: EmboCept DSM-TACE seems to be a safe treatment option in intermediate stage HCC
Larsen et al. 2019	Oxaliplatin 5-Fluorouracil	PES-related symptoms Mild increase in liver enzymes Conclusion: Well tolerated with few adverse events
Orlacchio et al. 2018	Doxorubicin	PES-related symptoms Non-surgical cholecystitis Prolonged hospitalization
Schicho et al. 2018	Mitomycin C Cisplatin Gemcitabin Oxaliplatin Irinotecan Epirubicin Doxorubicin	PES-related symptoms Sweating Diarrhea Shivering Ulcer (in between treatments)
Orlacchio et al. 2015	Doxorubicin	PES-related symptoms Conclusion: DSM-TACE represents a safely and effective treatment option with similar safety and efficacy of conventional chemoembolization
Schicho et al. 2017-2	Mitomycin C Gemcitabine Carboplatin	PES-related symptoms One patient died from hepatic failure AEs likely related to cytostatic: Thrombocytopenia Conclusion: Use of DSM as embolic agent is safe in terms of adverse and serious adverse events
Vogl et al. 2009-1	Mitomycin C Gemcitabine Irinotecan	PES-related symptoms
Vogl et al. 2012	Mitomycin C Gemcitabine Irinotecan	PES-related symptoms Conclusion: no major side effects or complications
Vogl et al. 2010	Mitomycin C Gemcitabine	PES-related symptoms Conclusion: TACE has a low complication rate
Vogl et al. 2011	Mitomycin C Gemcitabine	PES-related symptoms AEs likely related to cytostatic: Chemotherapy-associated steatohepatitis in the follow-up period Conclusion: The negligibility of major side effects or complications, the minimally invasive nature, and the capability of performing the treatment on an outpatient basis makes TACE with LITT a good therapeutic alternative in the care of patients not responding to systemic chemotherapy alone and as an alternative to surgery when liver resection is contraindicated.

Reference	Cytostatics	Reported AEs/Conclusions if available
Kirchhoff et al. 2007	Cisplatin Doxorubicin	Focal liver necrosis Gastric ulcer Cholecystitis One patient died one week after TACE in an extern hospital presumably from liver failure. AEs likely related to cytostatic: Partial dissection of the hepatic artery during angiography Reversible leukopenia and thrombocytopenia
Eichler et al. 2013	Gemcitabine	PES-related symptoms Conclusion: TACE with gemcitabine appears to be a safe and effective treatment
Iezzi et al. 2018	Epirubicin	Increased serum level of transaminases Transient cholecystitis Conclusion: TACE with degradable starch microspheres (DSM-TACE) is safe and effective as second-line treatment
Carr et al. 1997	Doxorubicin Cisplatin	Hepatitis Pancreatitis Dyspnoea/hypotension Hepatic artery occlusion after several treatment cycles Toxicities included death, one patient (and a death of uncertain cause in an additional patient) Conclusion: DSM appears to be a promising adjunct to intrahepatic artery chemotherapy because of its safety and hepatic tolerance
Nabil et al. 2008	Mitomycin C Gemcitabine	PES-related symptoms AEs related to procedure: Puncture site hematoma
Lorenz et al. 1989	Mitomycin C	PES-related symptoms Dyspnoea Bradycardia Conclusion: Side effects were difficult to handle.
Thulin et al. 1986		Shunting with cyanosis Systolic blood pressure drop
Gruber-Rouh et al. 2018-1	Mitomycin C	PES-related symptoms Conclusion: A prospective randomized study would be more accurate to assess treatment safety
Niessen et al. 2014	Doxorubicin	PES-related symptoms Allergic reaction Hematoma AEs related to procedure: Accidental perforation of a side branch of the phrenic artery Conclusion: Chemoembolisation represents an alternative method of HCC treatment with a safety profile similar to that of conventional transarterial chemoembolisation

Reference	Cytostatics	Reported AEs/Conclusions if available
Minici et al. 2021	Doxorubicin	PES-related symptoms Non-surgical cholecystitis Conclusion: DSM-TACE is effective and safe in intermediate-stage HCC, achieving an interesting downstaging rate
Gross et al. 2020	Doxorubicin Epirubicin	PES-related symptoms Duodenal ulcer (could be caused by an incorrect cannulation of guide-wire or a prevented blood supply of duodenal Conclusion: DSM-TACE of HCC is safe even in patients with advanced disease stages
Gruber-Rouh et al. 2018-2	Mitomycin C Irinotecan	PES-related symptoms Conclusion: A prospective randomized study would assess treatment safety and efficacy of TACE with mitomycin and irinotecan more accurately
Haubold et al. 2020	Doxorubicin	complication: % CIRSE 1°: 11% CIRSE 2°: 9% CIRSE 3°: 2% CIRSE 4°–6°: 0% Complications that occurred during or after 134 DSM-TACE interventions according to CIRSE guidelines. Conclusion: DSM-TACE appears to be a safe, well-tolerated, and effective treatment option
Goerg et al 2019	Cisplatin Doxorubicin Mitomycin C	PES-related symptoms Asymptomatic peribiliary necrosis Bile duct necrosis and hepatobiliary abscess two deaths (are not related to the product (treatment error in one case, cardiac arrest before TACE in the second case) Conclusion: Considering the increased risk of peribiliary necrosis and subsequent hepatobiliary abscess development, precautionary measures should be strongly considered, especially in patients with a bilioenteric anastomosis
Auer et al. 2020	Doxorubicin	PES-related symptoms Conclusion: DSM-TACE has a better safety profil regarding AEs compared to SIRT
Gruber Rouh et al. 2014	Mitomycin C Irinotecan Gemcitabine Cisplatin	PES-related symptoms Conclusion: No major complications were encountered. TACE was performed successfully in all patients with no mortality and a low morbidity rate.
Zangos et al. 2001	Mitomycin C	PES-related symptoms Conclusion: All patients tolerated TACE well with local anaesthesia and intravenous pain therapy
Vogl et al. 2009-2	Mitomycin C Gemcitabine	PES-related symptoms Conclusion: Only minor side effects occurred, and no major complications developed
Wasser et al. 2005	Mitomycin C	PES-related symptoms Increased transaminases Gastric ulcer Cholecystitis Conclusion: Complications of TACE seem to be rare, but should not be underestimated

Reference	Cytostatics	Reported AEs/Conclusions if available
Ishida et al. 2008	Mitomycin C 5-fluorouracil Cisplatin l-leucovorin	PES-related symptoms Duodenal ulcer AEs likely related to cytostatic: Thrombocytopenia Leukopenia AEs related to procedure: Infection of the reservoir port Conclusion: functional status (in terms of activities of daily living) of all patients remained relatively good

5.4 An overall summary of clinical performance and safety

EmboLog® S has been assessed to be a clinically proven medical device.

The medical device occludes liver vessels to optimize the intra-tumoural drug accumulation of liver tumours. The therapeutic benefit of the medical device is based on an improved efficacy and safety, especially an improved tumour response and a prolonged survival. Embolization enhances the effects of chemotherapy and limits systemic toxicity. The side-effects of degradable starch microspheres are mainly mild and transient. Postembolization syndrome is frequent but transient and can be resolved by medication without further complications. Major complications are rare or are more related to the cytostatic drugs. The instructions for use proposed by the manufacturer cover the hazards and other clinically relevant information that may have an impact on the use of the device. Consequently, the risk-benefit ratio for the medical device is favourable. The essential requirements regarding clinical performance and safety are met.

5.5 Ongoing or planned post-market clinical follow-up

Clinical Evaluation Report of EmboLog® S has concluded that for the indications stated in the IFU, the evidence presented is adequate to support the long-term safety and performance of subject device. In order to institute and to keep up to date the clinical experience with the device for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions a post marketing follow up plan was established.

The post-market clinical follow-up includes the following activities:

- Screening of scientific literature
- Screening of clinical study registers
- Screening of adverse event databases
- PMCF Survey

6 Possible diagnostic or therapeutic alternatives

The BCLC classification is used to classify the severity of the disease, taking into account the often-accompanying liver cirrhosis. Therapy recommendations can be derived from the BCLC-classification:

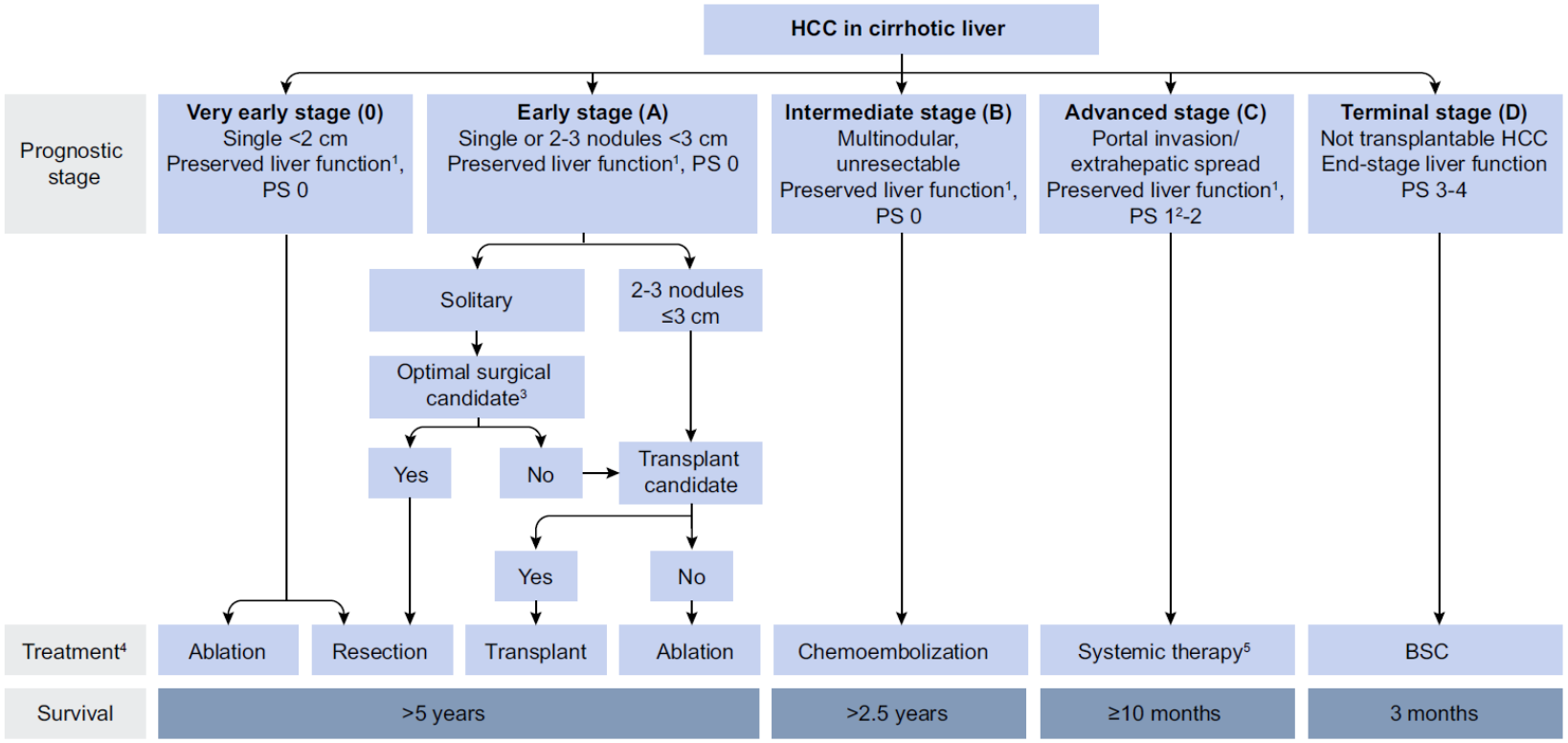

Figure 1 Modified BCLC staging system and treatment strategy [European Association for the Study of the Liver, 2018]

Staging systems for clinical decision making in HCC should include tumour burden, liver function and performance status. Once the diagnosis is established, prognostic assessment is a critical step in the management of hepatocellular carcinoma (HCC). Cancer classification is intended to establish prognosis and enables the selection of the adequate treatment for the best candidates.
Surgical resection is recommended as treatment of choice in patients with HCC arising on a non-cirrhotic liver (evidence low; recommendation strong).
Liver transplantation (LT) is recommended as the first-line option for HCC within Milan criteria but unsuitable for resection (evidence high; recommendation strong). Milan criteria are the benchmark for selection of patients with HCC for LT and the basis for comparison with other suggested criteria [European Association for the Study of the Liver, 2018].
Thermal ablation with radiofrequency is the standard of care for patients with BCLC 0 and A tumours not suitable for surgery (evidence high; recommendation strong). Thermal ablation in single tumours 2 to 3 cm in size is an alternative to surgical resection based on technical factors (location of the tumour), hepatic and extrahepatic patient conditions [European Association for the Study of the Liver, 2018].
TACE is recommended for patients with BCLC stage B and should be carried out in a selective manner (evidence high; recommendation strong). Sorafenib is the standard first-line systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A) and with advanced tumours (BCLC–C) or earlier stage tumours progressing upon or unsuitable for loco-regional therapies (evidence high; recommendation strong) [European Association for the Study of the Liver, 2018]. Chemoembolization offers the ability to expose tumours to high local chemotherapeutic agent concentrations with minimal systemic drug bioavailability.
In HCC on cirrhosis, acetaminophen (paracetamol) up to 3 g/day can be utilised for the management of pain of mild intensity. Non-steroidal anti-inflammatory drugs should be avoided whenever possible in patients with underlying cirrhosis. Opioids can be utilised for the management of pain of intermediate or severe intensity, paying attention to proactively avoid constipation (evidence low; recommendation weak). [Auer et al. 2020]

7 Suggested profile and training for users

For the safe use of EmboLog® S the administration has to be done by specialist physicians trained in vascular embolization procedures.

8 Reference to any harmonised standards and CS applied

Common	
DIN EN ISO 9001:2015-11	Quality management systems. Model for quality assurance/QM documentation in design, development, production, assembly and, maintenance
DIN EN ISO 13485:2016-08	Medical devices – Quality management systems – Requirements for regulatory purposes
DIN EN ISO 14971:2020-07	Medical devices. Application of risk management to medical devices
ISO/TR 24971:2020-06	Medical Devices- Guidance on the application of ISO 14971
MPDG	German Law on Medical Devices
MDR	Medical Device Regulation (EU) 2017/745
	EU GMP Guidelines
	European Pharmacopoeia – current version

Biological and Clinical Evaluation	
DIN EN ISO 10993-1:2021-05	Biological evaluation of medical devices – Part 1: evaluation and testing
DIN EN ISO 10993-4:2017-12	Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood
DIN EN ISO 10993-5:2009-10	Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity
DIN EN ISO 10993-10: 2014-10	Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization
DIN EN ISO 10993-11:2018-09	Biological evaluation of medical devices - Part 11: Tests for systemic toxicity
ISO 10993-12:2021	Biological evaluation of medical devices - Part 12: Sample preparation and reference materials
MEDDEV. 2.7.1 rev.04	Clinical evaluation of medical devices
ISO/TR 20416:2020-07	Medical devices — Post-market surveillance for manufacturers

Sterilization	
DIN EN ISO 17665-1:2006-11	Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation and routine control of a sterilization process for

	medical devices
	EU GMP Guidelines
	European Pharmacopoeia – current version

Cleanrooms and microbiological monitoring	
EU-GMP-Guideline Part 1	EU-Good Manufacturing Practice (GMP) guidelines – Part I - Basic Requirements for Medicinal Products
EU-GMP-Guideline Annex 1	EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 1 Manufacture of Sterile Medicinal Products
DIN EN:ISO 14644-1:2016-06	Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration
DIN EN ISO 14644-2:2016-05	Cleanrooms and associated controlled environments – Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration

Labeling	
DIN EN ISO 15223-1:2022-02	Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements
DIN EN ISO 20147:2021	Information to be supplied by the manufacturer of medical devices

Usability	
DIN EN 62366-1:2021-08	Application of usability engineering to medical devices

9 List of abbreviation

Abbreviation	Definition
BCLC	Barcelona Clinic Liver Cancer
BSA	Body surface area
BSC	Best supportive care
CIRSE	Cardiovascular and Interventional Radiological Society of Europe
CS	Common specification
DSM	Degradable Starch Microspheres
EU	European Union
GMP	Good manufacturing practise
HAT	Hepatic arterial therapy
HCC	Hepatocellular Carcinoma
IFU	Instruction For Use
LITT	Laser-induced thermotherapy
LT	Liver Transplantation
MBC	Metastatic breast cancer
MEDDEV	Medical Device guidance
MDCG	Medical device coordination group
MDR	Medical Device Regulation
OS	Overall Survival
PES	Post-embolization Syndrome
PS	Prognostic stage
PMCF	Post Market Clinical Follow-up
PMS	Post Market Surveillance
SSCP	Summary of Safety and Clinical Performance
TACE	Transarterial Chemoembolization

10 Revision History

SSCP revision number	Date issue	Change description	Revision validated by the Notified Body	Date of Notified Body Approval
001	2023-08-16	Initial release	☐ Yes Validation language: English ☐ No	

Internal revision history before initial release (will not be included in the published SSCP)

Date	Rev-No.	Author	Description of Change
2021-01-14	0001-00	Linda Geringswald	First edition
2021-07-22	0001-01	Linda Geringswald	Update acc. MDR 2017/745

2021-10-28	0001-02	Linda Geringswald	Update/Change acc. IFU: - 2.1 Intended Purpose, - 2.2 Indication - Dosage/Administration - 3.5 Description of any other devices (contact address, reference book) - 4.1 Residual risks and undesirable effects - 4.2 Warnings and Precaution - 5.1- Summary of clinical data related to equivalent device (basis of clinical evaluation report) - 5.3 Summary of clinical data from other sources - 5.4 An overall summary of clinical performance and safety - Addition of chapter 2.4 Dosage and Administration - 8 Harmonised Standards CS
2023-08-16	0001-03	Lisa Joachimi	- Deletion of section 2.4 (no required paragraph acc. to MDCG 2019-9 - Deletion of indication “lung tumour therapy” In sections 2, 4, 5, 6 - Comprehensive revision of sections 5.3, 5.5 - Update references in section 10 - Minor changes in complete document - Addition of revision history acc. to MDCG 2019-9, changes in internal revision numbering - Addition of list of abbreviations

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