Title		
Summary of Safety and Clinical Performance		
Document number D10419	Project number -	Unique ID 01
Approved: Date/Sign 2023-10-25 Charlotte Woschnagg Author, Charlotte Woschnagg		Katarina Åsberg Approved, Katarina Åsberg

1. Purpose

The purpose of this document is to present the Summary of Safety and Clinical Performance (SSCP) for M Dialysis AB's class III MDR devices. It shall be made available to the public via Eudamed by the Notified Body after validation.

2. Identification of device and manufacturer

Devices covered by this SSCP includes:

- **Brain Microdialysis Catheter**:
  - 70 Brain Microdialysis Catheter 60/10 (REF: P000049)
  - 70 Brain Microdialysis Catheter 60/20 (REF: P000080)
  - 70 Brain Microdialysis Catheter 100/10 (REF: P000050)
  - 71 High Cut-Off Brain Microdialysis Catheter 60/10 (REF: 8010320)
  - 71 High Cut-Off Brain Microdialysis Catheter 60/20 (REF: 8010331)
  - 71 High Cut-Off Brain Microdialysis Catheter 60/30 (REF: 8010337)

- **Brain Microdialysis Bolt Catheter**:
  - 70 Microdialysis Bolt catheter 130/10 (REF: P000131)
  - 71 High cut-off Microdialysis Bolt Catheter 130/10 (REF: 8010954)

Manufacturer: M Dialysis AB

Address: Hammaby Fabriksväg 43, 120 30 Stockholm, Sweden

SRN: SE-MF-000017466

Basic UDI-DI (Microdialysis Sampling System Brain, in which the devices are included): 7332699_360_002_YA

EMDN: F05 (Devices for Microdialysis of Specific Organs)

Notidied Body: Intertek Medical Notified Body AB (NB 2862)

Basic UDI-DI for individual devices (Table 1):

Variant	**Article number** **Basic-UDI** **EMDN** **Risk Class**	**Differences**
Brain Microdialysis Catheter		
70 Brain Microdialysis Catheter 60/10	P000049 7332699_320_001_W3 F05 III	Different lengths on shaft and membrane. Different pore sizes (regular and high cut-off membrane)

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70 Brain Microdialysis Catheter 60/20	P000080 7332699_320_001_W3 F05 III	
70 Brain Microdialysis Catheter 100/10	P000050 7332699_320_001_W3 F05 III	
71 High Cut-Off Brain Microdialysis Catheter 60/10	8010320 7332699_320_001_W3 F05 III	
71 High Cut-Off Brain Microdialysis Catheter 60/20	8010331 7332699_320_001_W3 F05 III	
71 High Cut-Off Brain Microdialysis Catheter 60/30	8010337 7332699_320_001_W3 F05 III	
Brain Microdialysis Bolt Catheter		
70 Microdialysis Bolt catheter 130/10	P000131 7332699_320_002_W6 F05 III	Different lengths on shaft and membrane. Different pore sizes (regular and high cut-off membrane)
71 High cut-off Microdialysis Bolt Catheter 130/10	8010954 7332699_320_002_W6 F05 III	

Table 1: Product codes

3. Intended purpose

Microdialysis Sampling System, Brain

The Microdialysis Sampling System is intended to enable microdialysis of the interstitial fluid of tissues and blood.

Brain Microdialysis Catheter

The Brain Microdialysis Catheter is intended to enable microdialysis of the extracellular (interstitial) fluid of the brain tissue.

Brain Microdialysis Bolt Catheter

The Brain Microdialysis Bolt Catheter is intended to enable microdialysis of the extracellular fluid of the brain tissue

3.1. Indications

The Brain Microdialysis Catheter is indicated for patients with clinical signs of brain injury or brain disease where craniotomy is required for diagnosis or therapy e.g. monitoring of ischemia in patients suffering traumatic brain injury (TBI) and subarachnoid haemorrhage (SAH). Microdialysis shall not be used as the sole basis for diagnosis or therapy.

The Brain Microdialysis Bolt Catheter is indicated for patients with clinical signs of brain injury or brain disease where craniotomy is required for diagnosis or therapy e.g. monitoring of ischemia in patients suffering traumatic brain injury (TBI) and subarachnoid haemorrhage (SAH). Microdialysis shall not be used as the sole basis for diagnosis or therapy

3.2. Contraindications

Brain Microdialysis Catheter/ The Brain Microdialysis Bolt Catheter:

- Patients with coagulopathy, increased susceptibility to infections or bleeding disorders.
- Patients on anticoagulant drug therapy.
- When monitoring patients with brain tumors there could be a possibility of dissemination of tumor cells.
- Inserting the catheter into the brain may cause bleeding from damaged vessels.
- Leakage of cerebrospinal fluid may occur at the site of skin penetration
- Patients with known hypersensitivity to Dextran (71 High Cut-off Brain Microdialysis catheter and 71 High Cut-off Bolt Microdialysis catheter).

3.3. Target populations

There are no limitations regarding patient population. Microdialysis shall not be used as the sole basis for diagnosis or therapy.

4. Description of device

The device is used together in a Microdialysis Sampling System (see chapter 4.2 for more information) in which the Brain Microdialysis Catheter/Brain Microdialysis Bolt Catheter is placed in the brain tissue where microdialysis is performed. The catheter consists of an inlet tube, which is connected to the syringe in the pump, a membrane functioning as an artificial blood vessel and an outlet tube with a microvial holder, where the sample can be collected in. The microvial is exchanged regularly by the hospital staff and brought for analysis.

The 70 Microdialysis Catheter/71 High Cut-Off Microdialysis Catheter is tunnelated under the scalp with a tunnelating needle. It is then inserted with the help of microdialysis forceps into the brain tissue through a hole drilled in the skull bone.

The 70 Microdialysis Bolt Catheter / 71 High cut-off Microdialysis Bolt Catheter is designed for microdialysis in brain tissue by using a commercially available bolt, into which the catheter is attached using the bolt incorporated onto the catheter shaft.

The tip of the catheter contains a gold thread, which makes it visible on a CT-scan to locate the exact position of the catheter in the brain.

4.1. Previous generation(s)/variants

The catheters have been available in different variants on the EU market under MDD CE mark since 1997, originally under the brand name CMA 70 / CMA 71. There have been no product changes of the MDR products compared to the MDD products.

4.2. Accessories / devices used in combination

The device is used together in a Microdialysis Sampling System, which consists of a **Microdialysis pump** (class IIa), which, by the means of a **Syringe** (class IIa), pumps sterile **Perfusion fluid** (class IIa) through the **Microdialysis Catheter**. Insertion of the catheter into certain target tissues is simplified using a **Tunnelating needle** (class Ir) and **Forceps** (class Ir)**:**

- Microdialysis pump
  - 106 Microdialysis pump (fixed flow rate) (REF: P000003)
  - 107 Microdialysis pump (adjustable flow rate) (REF: P000127)
- 106 Syringe (REF: 8010191)
- Perfusion fluid
  - Perfusion fluid CNS (REF: P000151)
  - Perfusion fluid CNS Dextran (REF: 8050151)
- Tunnelating Needle (REF: P000055)
- Forceps (REF: P000056)

5. Possible diagnostic or therapeutic alternatives

Example of other monitoring of the brain tissue:
-Parenchymal Tissue ICP sensor
-Tissue PO_2 sensors

Example of other global brain monitoring:
-ICP monitoring via ventricular drain

Example of non-invasive brain Monitoring (device placed on the head):
-Transcranial doppler

6. Harmonized standards

The devices are in compliance with or are manufactured according to the following standards:

- EN ISO 13485:2016 Medical Devices – Quality management system – Requirements for regulatory purposes
- ISO 14971:2019 Medical devices - Application of risk management to medical devices
- IEC 62366-1:2015 + A1:2020 Medical devices - Part 1: Application of usability engineering to medical devices
- EN ISO 10993-1:2020 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process
- EN ISO 10993-3:2014 Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- EN ISO 10993-5:2009 Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity
- EN ISO 10993-6:2016 Biological evaluation of medical devices - Part 6: Tests for local effects after implantation
- EN ISO 10993-10:2013 Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization
- EN ISO 10993-11:2018 Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (ISO 10993-11:2017)
- EN ISO 10993-17:2009 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances (ISO 10993-17:2002).
- EN ISO 10993-18:2020 Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process
- ISO 11607-1:2019 Requirements for materials, sterile barrier systems and packaging systems
- ISO 11607-2:2019 Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes
- SS-EN ISO 11737-1:2018 Sterilization of medical devices – Microbiological methods – Part 1: Determination of a population of microorganisms on products
- EN ISO 11137-1:2015 Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices
- EN ISO 11137-2:2015 Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose
- EN 556-1: 2001/AC:2006 Sterilization of medical devices – Requirements for medical devices to be designated “STERILE” – Part 1: Requirements for terminally sterilized medical devices
- ISO 14644-1:2016 Clean rooms and associated controlled environments - Part 1: Classification of air cleanliness by particle concentration
- ISO 14644-2: 2016 Clean rooms and associated controlled environments - Part 2: Specifications for testing and monitoring to prove cont. compliance with ISO 14644-1
- SS-EN ISO 14644-5: 2004 Cleanrooms and associated controlled environments - Part 5: Operations
- ISO 14698-1:2003 Clean rooms and associated controlled environments – Bio contamination control -- Part 1: General principles and methods
- ISO 14698-2:2003 Clean rooms and associated controlled environments – Bio contamination control -- Part 2: Evaluation and interpretation of bio contamination data
- SS-EN ISO 15223-1:2021 Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements
- SS-EN ISO 20417:2021 Medical devices — Information to be supplied by the manufacturer

7. Clinical evaluation

7.1. Summary of clinical evaluation and equivalence

The system is the same as previously CE marked system under MDD hence it is equivalent to that device in all aspects technical, biological, and clinical and hence all published clinical data can be reused in this review.

7.1.1. Devices included in this clinical evaluation file

The catheter(s) is a part of a system with several components as described above. To get clinical data, the complete system must be considered when doing this clinical evaluation.

7.1.2. Scientific Validity

The system has been clinically used for many years and is a well-established clinical tool and is included in the state of the art in medicine. The scientific validity has been demonstrated through a combination of a review of relevant literature together with a systematic literature review using peer-reviewed literature. The safety of the device is confirmed by using applicable state of the safety standards.

The microdialysis device in not a stand-alone method. It is mainly used in combination with other well established methods for multimodality surveillance of patients and human organs, providing important information on the temporal evolution of important clinical events or complications to reduce the risk of morbidity and mortality of the patients.

7.1.3. Scientific validity literature search summary

For this review the main data base used was PubMed database. In addition, additional searches in the BIOSIS, EMBASE, Global Health, Scopus, and Cochrane Library databases was used for identifying clinical studies using Microdialysis Catheters, Microdialysis Analysers (ISCUS^{flex}/ISCUS/CMA600) and perfusion fluids manufactured by M Dialysis AB. ISCUS and CMA 600 are previous generation of microdialysis analyzers, which are considered equivalent to ISCUS^{flex} in terms of analytical performance.

7.1.4. General methodology, data sources and search string

The PubMed database (NIH National Library of Medicine) was used. The search aimed at identifying clinical studies using the microdialysis device consisting of Microdialysis Catheters and Microdialysis Analysers (ISCUS, ISCUS flex and CMA600) and Microdialysis Perfusion Fluids (Perfusion Fluid T1 and Perfusion Fluid CNS), manufactured by M Dialysis AB, used for monitoring energy related metabolites (glucose, lactate, pyruvate, glycerol), glutamate and urea in human patients or healthy volunteers in a variety of clinical fields. Three complementary search strings were used on October 13, 2023; firstly “microdialysis AND lactate AND pyruvate AND glucose AND glycerol”, secondly “microdialysis AND glutamate” and thirdly “microdialysis AND urea”.

In the systematic reviews included in the analysis below the authors performed additional searches in the BIOSIS, EMBASE, Global Health, Scopus, and Cochrane Library databases.

7.1.5. Selection criteria

The report covers articles published 2000-August 24, 2023. Filters used were Clinical Study, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review.

Selection criteria for the identified literature allow for a first more comprehensive round of searching and a broader selection of which the results was filtered. Thus, missing relevant data could be avoided. Abstracts lack sufficient detail to allow thorough evaluation, but they are sufficient to allow a first evaluation of the relevance of a paper based on inclusion and exclusion criteria. Nevertheless, where possible the full text version of the article is preferred. During the appraisal, an overall conclusion if the literature is excluded has been determined as irrelevant with a short summary of why, based on the exclusion criteria:

- Application outside of intended use or indication
- Publication without relevance to the scientific validity for the system or parts therof under evaluation.
- Obvious methodological weaknesses.

7.1.6. Data collection

The data collection was done on August 24, 2023 by Prof. Lars Hillered, his qualifications are found in Appendix 1. All data retrieved was evaluated based on the publicly available content according to the search strings. For the items remaining after this selection full text versions were collected and stored in the software EndNote 20 (Clarivate.com).

The PubMed search aimed at identifying clinical studies using the microdialysis device consisting of Microdialysis Catheters and Microdialysis Analysers (ISCUS, ISCUS flex and CMA600) and Microdialysis Perfusion Fluids (Perfusion Fluid T1 and Perfusion Fluid CNS), manufactured by M Dialysis AB. The following search strings were used on August 24, 2023; firstly “microdialysis AND lactate AND pyruvate AND glucose AND glycerol”, secondly “microdialysis AND glutamate” and thirdly “microdialysis AND urea”. The searches performed on August 24, 2023, returned a total of 114 articles, 62, 37, and 15, for Search 1, 2, and 3, respectively. The identified articles were published 2000-2023.

7.1.7. Criteria for inclusion/exclusion

Since the purpose of this review was specifically to search for information about performance and safety of the applications, even studies with a small number of patients/healthy volunteers were included.

The following criteria were used for inclusion of articles:

a. Authors used microdialysis catheters manufactured by M Dialysis AB
b. Authors used dedicated microdialysis analyzers ISCUS, ISCUS flex or CMA600 manfactured by M Dialysis AB
c. Chemical analyses of microdialysate samples included glucose, lactate, pyruvate, glycerol, glutamate or urea
d. Authors collected microdialysis samples from human patients or subjects/healthy volunteers in their study

Only articles fulfilling all 4 criteria were accepted for further analysis in this literature review.

7.1.8. Summary of all available data and conclusions

In the field of neurosurgery/neurointensive care, the microdialysis monitoring has been used for more than 3 decades in a large number of patients (>3500 patients) and the device is currently regarded as an important part of the methodological arsenal used in neurointensive care for brain and patient surveillance (a.k.a. multimodality monitoring), providing important complementary information about the neurochemical status of the acute brain injury with a favorable risk-benefit ratio. In the articles on cerebral microdialysis use in neurointensive care important new information has been gained sheading new light on the patho-biochemistry of acute brain inury, particularly traumatic brain injury (TBI), subarachnoid heorrhage (SAH) and intracerebral hemorrhage (ICH), constituting the bulk of patients treated in modern neurointensive care. This patho-biochemistry has been shown to correlate with patient outcome in statistical multivariate correlation analyses. Further studies may be needed to confirm the usefulness of microdialysis monitoring for recording of treatment effects, drug penetration to the brain and the development of individualized treatment protocols.

In the systematic review included in this review (6.1.12), the authors concluded that their review replicated the summary of literature of the 3 previously published consensus statements on cerebral microdialysis use in neurointensive care providing a basis for expert recommendations for use of cerebral microdialysis monitoring as a part of multimodality monitoring in neurointensive care.

The consensus article (6.1.17) written by 47 leading experts in the field aimed to combine literature review of the 680 articles published 2004-2014 with expert opinion. The article contains guidance for the use of microdialysis in traumatic brain injury and subarachnoid hemorrhage in neurocritical care, including clinical indications for use in TBI and SAH patients, catheter location and insertion techniques, reference values and interpretation of microdialysis data, as well as critical values and interventions. The authors conclude that cerebral microdialysis is a reliable and safe technique that is used in the clinical management of neurocritical care patients and in particular those with severe TBI or SAH. In addition, there are several research applications that are important for developing our understanding of brain physiology, pathophysiology and drug development.

In the other medical fields, microdialysis is considered a promising tool for bed-side monitoring of tissue ischemia (measuring dialysate glucose, lactate, pyruvate and glycerol) or inflammation (measuring dialysate glutamate) in various peripheral organs. The main intension is to monitor the clinical course of the patients to get early warning signals of emerging complications enabling timely intervention to avoid morbidity and mortality of the patients. The methodology is considered minimally invasive with a favorable risk-benefit ratio. For some applications the authors recommend confirmatory studies on larger patient samples before inclusion into routine clinical treatment protocols.

In the systematic review (6.1.7) the authors included twenty-six studies for analysis, involving a total of 702 patients in seven sub-fields of gastrointestinal (GI) surgery and intensive care. The authors found that most studies showed that levels of microdialysis biomarkers correlated with the postoperative clinical course. Lactate, pyruvate, glucose, and glycerol were the most frequently measured biomarkers. Several studies found that changes in biomarkers in complicated patients preceded symptoms of complications and changes in conventional clinical methods of postoperative monitoring. The studies were in general of low scientific quality, underpowered and non-randomized. In conclusion, microdialysis is a promising technique for postoperative monitoring of GI surgical patients. Larger randomized studies are needed to define the clinical implications of microdialysis.

7.2. Post-market clinical follow-up

The PMS and PMCF evaluation reports show that there have not been any major issues with the system in terms of complaints, vigilance reporting or product nonconformities during the last 5 years that has been reviewed.

7.2.1. Post Market Surveillance report

The report documents 4 complaints that have been categorized to be handling error. The information given does not suggest that this is user errors that directly are connected to the design of the product or usability.
The reviewed CAPAs are not described in the clinical data or other official documentation.

A search in the FDA Maude database do not give any hits on Microdialysis or its products.
Reported open issue are supplier deviations caused by delayed supplier delivery. There are no suggestions that this have had effects on the clinical use or effected the safety or performance of the product.

7.3. Summary of the performed analyses of the data

The analyses of the data show the following:

- There are no indications that product is not used as intended
- All input from public or other sources about hazards are covered in the risk analysis
- There are no indications that product functionality is no longer state-of-the-art
- There are no data that suggest that the design changes made have any effects on the performance of the products

8. Suggested profile and training for users

The Brain Microdialysis Catheter and Brain Microdialysis Bolt Catheter should be inserted by a Neurosurgeon. Connection of the catheter to the Microdialysis pump and sample collection should be performed by Medical professionals.

9. Information to user

9.1. Residual risks

No residual risks remain after risk control implementation.

9.2. Undesirable side effects

N/A

9.3. Warnings / Precautions

- Care must be taken to avoid needle stick injuries to reduce risk of exposure to contaminated blood.
- This device is sterile unless the package has been opened or damaged.
- If any visible damage is observed the catheter shall not be used.
- The Catheter shall only be used together with the accessories described in the IFU
- Be sure to handle the catheter carefully to avoid kinking or other damage, particularly after removal of the protection tube. avoid contact with the dialysis membrane.
- If there is a suspicion that the catheter has become unsterile prior to insertion the catheter shall not be used.
- The pump syringe connected to the catheter should not manually be flushed since that could damage the dialysis membrane.
- Check that liquid is being pumped through the catheter by inspecting the volume in the microvial **each time** the microvials are changed.
- If there is no fluid in the collected vial, start a flush on the pump: Open the lid, wait 3 seconds and close it again. Wait for the flush (5 minutes). Check that the tubing's are not kinked and that the microvial holder needle is correctly piercing the microvial membrane. If there is still no fluid in the collected vial, the dialysis membrane might be damaged, and the catheter must be removed.
- Remove the catheter if there is a permanent stop in the liquid flow.
- The Microdialysis Catheter is for single use only. If the device is re-used there is a risk for cross-contamination.
- In the event of any serious incident occurring in the relation to the device, this shall be reported without delay to M Dialysis and the competent authority of the member state where the incident happened.
- When using high cut off membranes to avoid ultrafiltration; the catheter should be used with a Perfusion fluid containing dextran or similar.
- Remove the catheter if there are any signs of infection.
- Microdialysis Brain/Bolt Catheter is biocompatible up to 30 days. It may though stop working earlier because of clogging, duration of use is up to 12 days referring to literature.

10. Change History

Change history:				
Ver.	Doc. No.	Date	By	Description
00	D10292	2022-10-24	Anna-Karin Andermo	First version. Risk management plan previously described in general terms in the risk procedure QW971
01	D10292	2023-10-19	Charlotte Woschnagg	Updated device description (EDMN, Basic UDI-DI, Risk Class) and section Clinical Equivalence. Version submitted to Intertek for validation of the English version.