EUROPEAN COMMISSION

Opinion in the context of the Clinical Evaluation Consultation Procedure (CECP)

Expert panels on medical devices and in vitro diagnostic devices (Expamed)

Contents

Scope of this expert opinion

This scientific opinion reflects the views of independent experts (MDR Article 106) on the clinical evaluation assessment report (CEAR) of the notified body. The advice is provided in the context of the clinical evaluation consultation procedure (CECP), which is an additional element of conformity assessment by notified bodies for specific high-risk devices (MDR Article 54 and Annex IX, Section 5.1).

The notified body is obliged to give due consideration to views expressed in the scientific opinion of the expert panel and in particular in case experts find the level of clinical evidence not sufficient or have serious concerns about the benefit-risk determination, the consistency of the clinical evidence with the intended purpose including the medical indication(s) or with the post-market clinical follow-up (PMCF) plan.

Having considered the expert views, the notified body must, if necessary, advise the manufacturer on possible actions, such as specific restrictions of the intended purpose, limitations on the duration of the certificate validity, specific post-market follow-up (PMCF) studies, adaption of instructions for use or the summary of safety and clinical performance (SSCP) or may impose other restrictions in its conformity assessment report.

In accordance with MDR Annex IX, 5.1.g., the notify body shall provide a full justification where it has not followed the advice of the expert panel in its conformity assessment report.

1 ADMINISTRATIVE INFORMATION

Date of reception of the dossier	19/08/2021
Notified Body number	2797
Internal CECP dossier #	2021-000205
Medical device type	This group of medical devices (acetabular inserts/cups) are part of a combination system for Total Hip Replacement.
Intended purpose	This group of medical devices is intended for use in primary and/or revision Total Hip Arthroplasty (THA) to alleviate pain and restore hip joint function.
Risk class / type	☒ class III implantable ☐ class IIb ARMP
Screening step: appropriate medical field / competence area	Orthopaedics, traumatology, rehabilitation, rheumatology: Joint replacements (hip, knee, shoulder)

PART 1 – DECISION OF SCREENING EXPERTS: NOTIFICATION OF NB AND COMMISSION REGARDING THE INTENTION TO PROVIDE AN OPINION

1.1 Decision of the screening experts

Table covers all three criteria, intended to support their consistent and conscientious application

Date of decision	12/09/2021
Screening panel decision	
Is there intention to provide a scientific opinion?	☒ **Yes** ☐ **No** ☐ **Insufficient information to reach a conclusion**
In case the information is found insufficient to reach a conclusion, please summarise the reasons: (see MRD Annex IX Section 5.1 point c)	
BRIEF TEXT (indicatively max. 150 words)	
In case there is intention to provide an opinion, please provide a short summary of the reasons	
This dossier is on a group of polyethylene acetabular inserts to be used with or without bone-cement fixation in total hip replacement. The majority of the devices have been previously certified and marketed under the directives. The devices have proven clinical safety and performance, and majority of the changes to the devices from the directives is not expected to affect the benefit-risk ratio of the devices. The X3 Rimfit Cups have undergone minor modifications with reduced rim and as a result of this a needed shift in the position of the vent holes. Moreover, the sterilization method has been changed from gas plasma to ETO, as has the Ultra High Molecular Weight Polyethylene (UHMWPE) consolidation method been changed. From preclinical testing, all have been mentioned to have no clinical negative effect. These minor modifications bring no critical elements to the device – and no further opinion is needed here. However, there has been a change to the PMMA spacer material grade for the Contemporary Flanged Cup. According to the Notified Body, the preclinical testing has demonstrated equivalent or better properties for the device and no adverse clinical performance as a result of this change is expected. However, the preclinical documentation regarding the changes in the PMMA spacers are not available, and we are unable to judge the degree of novelty of this device.	
In case there is *no* intention to provide an opinion, please provide a short summary of the reasons	
BRIEF TEXT (indicatively max. 150 words)	
Any other comments	
It has been complicated to get the individual device overview from the submitted documents, as several different devices are included in this dossier. This has influenced the decision-making, as no single decision for the entire dossier is possible.	

1.2 Assessment of the three criteria

Criterion 1: Novelty of device under assessment and possible clinical / health impact
1.1 Novelty of device and/or of related clinical procedure
☐ No novelty: Neither device nor clinical procedure is novel **X** Novelty: **Device** is novel ☐ Novelty: **Procedure** is novel
Contemporary Flanged Cup: Change of the PMMA spacer material grade. The specific information regarding the change and the reported outcomes of the preclinical testing (technical documentation), were not available.
Select level of novelty: ☒ Low level *or* ☐ Medium level *or* ☐ High level
Uncertainties related to novelty
No uncertainties are related to the modifications of the X3 Rimfit Cup. There are uncertainties regarding the PMMA material that comes with the Contemporary Flanged Cup.
1.2 Possible negative clinical / health impact resulting from novelty
Concerns to the quality / stiffness of the PMMA spacer – and by this it's potential influence on device fixation.
Estimated severity of clinical and/or health impact
Select severity of clinical/health impact: ☐ No clinical or health impact ☒ Minor clinical or health impact ☐ Moderate clinical or health impact ☐ Major clinical or health impact
Uncertainties related to clinical/health impact
Concerns to the quality / stiffness of the PMMA spacer – and by this the potential influence on device fixation.

Criterion 2: Scientifically valid health concerns leading to significantly adverse changes in the benefit-risk profile of a specific group / category of devices and relating to

a) **Component(s)**
b) **Source material(s)**
c) **Impact on health in case of failure of the device**

Information on health concerns may be provided by the expert panel secretariat or may be available to experts, e.g. scientific / clinical literature.

2.1 Information from Secretariat: *Information on valid health concerns of groups / categories of devices received from the Secretariat?*	☐ Yes ☒ No
2.2 Other information: *Did the screening experts have other information (e.g. from the scientific literature) on valid health concerns of groups / categories of devices?*	☐ Yes ☒ No

2.3 Reference to peer-reviewed publications/information sources:
In case other information was considered, please provide the references of relevant peer-reviewed scientific / clinical publications

ENTER REFERENCES HERE

In case information was used from either the Secretariat or other sources

2.4 Groups/categories of devices:
To which group / category of devices did the information relate?

BRIEF TEXT

2.5 Relationship to component(s), source material(s) or health impact in case of device failure

☐ Health concern(s) relates to **component(s)**
☐ Health concern(s) relates to **source material(s)**
☐ Health concern(s) relates to **impact on health in case of device failure**

2.6 Description of health concern(s):

BRIEF TEXT (indicatively max. 150 words)

2.7 Reliability of information:

BRIEF TEXT (indicatively max. 150 words)

2.8 Relevance of information:

Very relevant

2.9 Summary:

BRIEF TEXT (indicatively max. 150 words)

Criterion 3: Significant increase of serious incidents of a specific group / category of devices relevant for the device under assessment *(if information is available, it will ALWAYS be provided by the expert panel secretariat)*	
3.1 Information received from secretariat?	☐ Yes ☒ No
In case information on incidents was received from the Secretariat	
3.2 How relevant is this information for the device under assessment?	
BRIEF TEXT (indicatively max. 150 words)	
3.3 Summary:	
BRIEF TEXT (indicatively max. 150 words)	

1.3 Indication of appropriate thematic panel in case opinion is required

Indication of appropriate thematic panel and competence area		
	Expert panels	Medical and scientific/technical competence areas (these may correspond to sub-groups)
☒	**Orthopaedics, traumatology, rehabilitation, rheumatology**	☒ 1. Joint replacements (hip, knee, shoulder) ☐ 2. Spinal devices ☐ 3. Non-articulating devices, rehabilitation
☐	**Circulatory system**	☐ 1. Prosthetic heart valves and devices for heart valve repair ☐ 2. Cardiovascular stents (metallic and bio-resorbable) and vascular prostheses ☐ 3. Active implantable cardiac devices and electrophysiological devices ☐ 4. Structural interventions and new devices (e.g. LAA/PFO occluders, heart failure devices) ☐ 5. Cardiac surgery including extracorporeal membrane oxygenation, cardiopulmonary bypass devices, artificial hearts and left ventricular assist devices
☐	**Neurology**	☐ 1. Central and peripheral nervous system devices ☐ 2. Implants for hearing and vision (sensory recovery) ☐ 3. Neurosurgical devices
☐	**Respiratory, anaesthesiology, intensive care**	☐ Respiratory and anaesthetic devices
☐	**Endocrinology and diabetes**	☐ Endocrinology and diabetes devices
☐	**General and plastic surgery Dentistry**	☐ 1. Surgical implants and general surgery ☐ 2. Plastic surgery and wound care ☐ 3. Maxillofacial surgery & Devices for dentistry e.g. oral surgery, implantology, dental materials etc.
☐	**Obstetrics and gynaecology including reproductive medicine**	☐ Devices for obstetrics and gynaecology
☐	**Gastroenterology and hepatology**	☐ Devices for gastroenterology and hepatology
☐	**Nephrology and urology**	☐ Devices for nephrology and urology
☐	**Ophthalmology**	☐ Devices for ophthalmology

PART 2 – SCIENTIFIC OPINION BY THEMATIC PANEL / SUB-GROUP

2.1 Information on panel and sub-group

Date of opinion	22/10/2021
Expert panel name	Orthopaedics, traumatology, rehabilitation, rheumatology
Sub-group of expert panel	Loadbearing joint replacements

2.2 Summary of expert panel opinion

The applicant has submitted a Clinical Evaluation in accordance with the requirements of the Medical Device Regulation (EU) 2017 Article 61 and Part A of Annex XIV and informed by MEDDEV 2.7/1, Rev. 4 (June 2016) confirm compliance to the General Safety and Performance Requirements per MDR Annex I, when used as intended, for a group of acetabular polyethylene components for total hip arthroplasty.

- **Device description: The devices include previously CE marked components and one adaptation of an existing flanged cup version as novel device**
  - highly crosslinked polyethylene (HCLPE) acetabular insert in 0° and 10°, gas plasma sterilized, CE marked for use with an acetabular shell
  - next generation highly crosslinked ultra-high molecular weight polyethylene (UHMWP) acetabular insert in 0° and 10°, with elevated rim or 10° eccentric produced with either compression moulding (CM) or ram extrusion (RE) and available as either gas plasma or ethylenoxide (EtO) sterilized version, CE marked for use with an acetabular shell
  - a large-flanged UHMWPE cup version to be trimmed intraoperatively with 4 polymethylmethacrylate (PMMA) cement spacers, gas plasma sterilized, CE marketed for cement fixation
  - a small-flanged UHMWPE cup version for intraoperative trimming with 4 polymethylmethacrylate (PMMA) cement spacers, gas plasma sterilized, with a radiopaque stainless-steel wire for the visualisation of the cup-position, CE marketed for cementation fixation
  - **novelty:** an adaptation of the flanged UHMWPE cup with a further reduced flange to avoid intraoperative trimming, produced with either CM or ram extrusion RE, change in cement spacer material to an impact modified PMMA based polymer resin and a 1mm offset in blow hole geometry for the version with 2mm spacers, with a radiopaque stainless-steel wire for the visualisation of the cup-position, use of EtO sterilization
  - constrained UHMWPE acetabular inserts pre-assembled with a bipolar universal head replacement in an 0° and 10° version to be used with an acetabular shell, and an all-poly version for cementation, CE marketed

  All devices are – with product-specific nuances – indicated as acetabular component in primary and revision total hip replacement, whereas the constrained components should be used in patients with a high risk or recurrent dislocations.
- **Adequacy of clinical evidence assessment by notified body**

  The manufacturer has provided a comprehensive data review covering literature reports (inclusion period depending on device type, earliest 1999 to December 2019), data from 5 international

registries (Australian Orthopaedic Association National Joint Replacement Registry Report (AOANJRR), National Joint Registry of England, Wales, Northern Ireland and Isle of Man (NJR), The New Zealand Joint Registry (NZJR), Swedish Hip Arthroplasty Register (SHAR), Norwegian Arthroplasty Register (NAR)), post marketing surveillance date from 01/2013-11/2019 and Orthopaedic Data Evaluation Panel (ODEP) ratings ranging from 7A* to 13A*, all demonstrating an adequate safety and performance of the devices compared to similar systems and the state of the art. For the novelty device clinical data are lacking.

- **Sufficiency of clinical evidence:** The clinical evidence provided from the above sources is sufficient for the demonstration of adequate safety and performance of the CE marketed devices, for the novel device clinical data is lacking.
- **Consistency of clinical evidence with purpose / medical indication(s):** provided clinical data support the use of the above acetabular devices if used as intended.
- **Consistency of clinical evidence with PMCF (post-market clinical follow-up) plan:** There are no specific safety concerns, the manufacturer commits for standard post market surveillance activities including Screening of peer-reviewed scientific literature, evaluation of clinical data from registries and/or public databases, collection and review of post-market clinical investigation data and customer/user feedback. The expert panel however suggests a more complete coverage of European registries in order to more reliably detect safety signals from the intended market. The addition of non-European registries is a valid complementary measure.
- **Adequacy of Benefit-risk determination:** The CE marketed devices are comparable to other acetabular components used in primary or revision total hip arthroplasty. The constrained components have less favourable outcomes typical in the complex population necessitating this type of implant. For the novel device a clinical benefit-risk determination is not possible. Based on the provided pre-clinical material properties non-inferiority of the novel material can be assumed. The other modifications are minor or equivalence has been demonstrated, so that overall equivalence to the small-flanged version can be assumed.
- **Overall conclusions and recommendations on clinical evaluation:** Based on the provided data adequate safety and performance of all discussed acetabular components can be expected if used as intended.

2.3 Detailed aspects of the opinion as required by MDR Annex IX Section 5.1

Opinion of the expert panel on the specific aspects of the clinical evaluation assessment report of the Notified Body (CEAR)[1]
1. Overall opinion on the NB's assessment of the adequacy of the manufacturer's clinical evaluation report
For the novel adaptation of the flanged UHMWPE cup the manufacturer reports a change in PMMA spacer material grade from MDD certified product in the Exeter Contemporary flanged cups with cement spacers. The manufacturer claims that the preclinical testing has demonstrated equivalent or better properties for the device and no adverse clinical performance as result of this change is envisaged; for this claim a Clinical Evaluation Consultation Procedure (CECP) is required.

[1] According to Annex IX Section 5.1 of Regulation (EU) 2017/745 - Assessment procedure for certain class III and class IIb devices.

The manufacturer does not consider the change in the material to be novel, they claim that the change in materials for the spacer should not elicit any change in benefit risk for those devices. Overall, the manufacturer's summary of pre-clinical data demonstrates non-inferior performance of the novel material's properties performance, in consequence the change of the PMMA material should not elicit a change in clinical performance as the function of the spacer is largely passive once the cement has cured.

EtO sterilization and CM production of the inserts has only been introduced in 2019 with CE marketing of the changes implying equivalence. While the availability of clinical data is limited, all the more since both literature review and data from arthroplasty registries only cover 2019, the relevance of these changes is not within the scope of the requested expert panel opinion.

The screening experts however have expressed some concerns in relation to the change to the PMMA spacer material grade for the Contemporary Flanged Cup, in particular on the quality and stiffness of the PMMA spacer – and by this its potential influence on device fixation. Thus, a scientific opinion was requested.

2. Opinion on the NB's assessment of the sufficiency of the clinical evidence provided by the manufacturer

The screening experts have expressed concerns regarding the equivalence of the PMMA spacers used in the novel adaptation of the flanged acetabular insert version. The manufacturer has provided detailed test results of material testing including PMMA spacer pull out-strength, tensile modulus, ultimate tensile strength, elongation at break, flexural modulus, flexural strength, izod impact strength, average ageing testing and 5-year shelf-life assessment.

These data have been provided by the manufacturer (CER_Annex (3320854).pdf), a document that covers:

Contemporary Cement Spacer Retention Protocol / Report (January 4, 2019)

Material Testing Summary for Material Change PMMA standard to novel (April 22, 2019)

Comparative analysis of PMMA standard versus PMMA novel mechanical properties (November 11, 2019)

The manufacturer reports in the CER Annex table 2 the results of the characterisation of the two materials. They report a Flexural Modulus of 2048 ± 56 MPa for original, and 2143 ± 104 MPa for the novel PMMA material. In general, the novel material slightly stiffer and stronger than the original one, but the differences are quite small. Accelerated aging tests show no significant degradation of mechanical properties the novel PMMA material.

The only pre-clinical test that the manufacturer performed to support the equivalence claim is the measurement of the mean retention force of the novel PMMA spacer material in comparison to the previously used one. Such test confirmed that the average retention force for novel spacers is higher (49 N) than that of original one (33 N), although these differences are not statistically significant.

The provided non-clinical data on material properties are considered adequate for the stated purpose. The change in PMMA material is not expected to change the safety or performance of the device. The further adaptations (with exception of the blow hole geometry) reported by the manufacturer have been previously CE marketed for other devices under MDD and are not within the scope of this scientific opinion:

- use of CM or RE with CM being non-inferior to RE as standard procedure (Wahyudi M et al 2018, IOP Conf. Ser.: Mater. Sci. Eng). An acetabular insert with these modes of production has been CE marketed in 2019.
- reduction of the flange size to avoid intraoperative trimming without expected negative impact, the relevance of the flange for cement impaction and long-term

results remains unclear (Fernandez-Valencia et al. 2016, European Journal of Orthopaedic Surgery & Traumatology).
- EtO sterilization with demonstrated non-inferiority to gas plasma sterilization. An acetabular insert with this type of sterilization has been CE marketed in 2019.
- 1mm offset of blow holes to avoid air trapping during cementation in the insert version with PMMA spacers (no change of geometry for insert version with 3mm) without expected impact on the cementation.

3. The NB's assessment of the adequacy of the manufacturer's benefit-risk determination

The manufacturer has provided the material testing data. In view of this information the panel does not share the screening experts' concern on the equivalence of the spacer material as in our opinion the biomechanical properties of the two spacers are equivalent, and thus we do not expect this specific modification to influence the fixation of the device.

The panel assumes that technical stability data for the already CE-marketed devices have been reviewed in the context of the 2019 CE marketing process and considers this evaluation as out of scope of the present scientific opinion. The behaviour *in vivo* will have to be closely monitored using registries, literature reviews and customer/user feedback or other appropriate methodological approaches.

After careful review of the documentation provided by the manufacturer, all members of the panel agree with agree with the NB's assessment of the manufacturer's benefit-risk determination for the change in PMMA spacer material grade.

4. The NB's assessment of the consistency of the manufacturer's clinical evidence with the intended purpose, including medical indication(s)

Overall, the panel perceives the manufacturer's clinical evidence as consistent with the intended purpose.

5. The NB's assessment of the consistency of the manufacturer's clinical evidence with the PMCF plan

The manufacturer envisions annual PMFC update activities including

- screening of peer-reviewed scientific literature with appraisal according to standard methodology
- evaluation of clinical data from registries and/or public databases, i.e.:
  - American Joint Replacement Registry
  - Australian Orthopaedic Association National Joint Replacement Registry
  - Belgian National Arthroplasty Register
  - Canadian Joint Replacement Registry
  - Danish Hip Arthroplasty Register
  - Dutch Arthroplasty Register
  - German Arthroplasty Register (EPRD)
  - National Joint Registry for England, Wales, Northern Ireland and the Isle of Man
  - New Zealand Joint Registry
  - Norwegian Arthroplasty Register
  - Swedish Hip Arthroplasty Register
- collection and review of post-market clinical investigation data (several longitudinal studies are ongoing currently)

- customer/user feedback surveys will be collected in accordance with D00035, Procedure for Post Market Surveillance, until D07326, Procedure for Cumulative Post Market Surveillance Activities, supersedes D00035
- continued suitability of the PMCF Plan will be assessed as each clinical evaluation is conducted per D01482, and the PMCF plan will be modified if necessary

The panel concurs with the NB's assessment report in regard to the proposed activities and frequency as adequate given the current data reported by the manufacturer on the preclinical testing of the alternative PMMA in form of spacers. As suggested above the more complete coverage of European registries should be considered.

2.4 Overall conclusions and recommendations

Overall conclusions and recommendations on clinical evaluation
After the evaluation of the provided data, the expert panel concurs with the NB's assessment of the manufacturer's conclusions on benefit-risk determination for the change in PMMA spacer material grade. Longitudinal monitoring of clinical outcomes as proposed in the manufacturer's PMCF plan is considered adequate to detect unexpected mechanisms of failure, insufficient performance, and a survival rate below the acceptable rate for clinical excellence.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[2]
Has the Secretariat provided information from stakeholders?
☐ Yes ☒ No
If yes, please summarise the information that was taken into account and describe briefly how it was taken into account.
Not applicable

2.6 Divergent positions in case no consensus could be reached

In case no consensus on the opinion could be achieved[3], please summarise divergent positions

[2] According to Article 106.4 of Regulation (EU) 2017/745, expert panels shall take into account relevant information provided by stakeholders including patients' organisations and healthcare professionals when preparing their scientific opinions.

[3] According to Article 106.12 of Regulation (EU) 2017/745, when adopting its scientific opinion, the members of the expert panels shall use their best endeavour to reach a consensus. If consensus cannot be reached, the expert panels shall decide by a majority of their members, and the scientific opinion shall mention the divergent positions and the grounds on which they are based.

Individual panel members stated the following concerns about adaptations of the device unrelated to the PMMA material:

Major changes in UHMWPE manufacturing ("novel aspects", CEAR document, page 37): changes in the raw material processing **from compression molding (CM) to ram extrusion (RE)** and sterilization **from gas plasma to ethylene oxide (EtO) may have clinically significant influence on future clinical performance of polyethylene** (different oxidation/chemical evolution and mechanical properties). Changes have been analyzed only in biomechanical preclinical studies (edge-loading of verticalized cup working along several millions of cycles in a test-device).
Nevertheless, another PE insert for uncemented cups from the manufacturer including the same changes (RE, EtO sterilization), is CE approved since December 2019 (page 6, 10, 11 and 14 of CEP document). It has been marketed with successful short-term use with data on clinical performance after only two years of implantation.

Medium changes in rim / flange diameter will force surgeons to modify the implantation technique. Pressurization of the new cup will push it until the bottom of acetabulum. The absence of the rim may provide an advantage (absence of anterior or posterior acetabular wall) but also a disadvantage (acetabular protrusion). A new surgical technique **may have a definitive influence on the final cup position**.

Additional comments:

Although not requested, the whole expert panel would like to underline that the submission of numerous devices for approval in the same dossier and its structure have been perceived counterproductive for an efficient review in particular since part of the standard mandate of panels is to provide advice on the consistency of clinical evidence with the purpose including the medical indications.

Please indicate how many of the experts of the panel or sub-group had divergent views
2/9 (as detailed in section 2.6)