EUROPEAN COMMISSION

Expert decision and 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.

ADMINISTRATIVE INFORMATION

Date of reception of the dossier	04/02/2025
Notified Body number	NB 1434
Internal CECP dossier #	EMA/EX/0000248787
Medical device type	Structures filling, replacement and reconstruction devices
Intended purpose	Intraarticular joints viscosupplementation
Risk class / type	☒ class III implantable ☐ class IIb active device intended to administer or remove medicinal products(s)
Screening step: medical field / competence area	Orthopaedics, traumatology, rehabilitation, rheumatology

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	17/02/2025
Screening panel decision	
Is there intention to provide a scientific opinion?	☒ **Yes** ☐ **No** ☐ **Insufficient information to reach a conclusion**
In case the information was found insufficient to reach a conclusion: summary of reasons (see MDR Annex IX Section 5.1 point c)	
N/A	
Summary as to why there is intention to provide an opinion	
There is a possible health impact relating to the addition of 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC) to hyaluronic acid, linked to the potential aggregation of phosphatidylcholine within the joint, thus affecting the joint function. Indeed, lecithin and hyaluronic acid have only been used in combination to prepare wound dressing foils.	
Summary as to why there is *no* intention to provide an opinion	
N/A	
Any other comments	
N/A	

1.2 Assessment of the three screening criteria

Criterion 1: Novelty of device under assessment and possible clinical / health impact
1.1 Overall degree of novelty
☐ No novelty: Neither device nor clinical procedure is novel ☐ Low level of novelty ☒ Medium level of novelty ☐ High level of novelty
Short description of the novelty, including main dimension(s) of novelty
The medical device is a viscoelastic gel composed of sodium hyaluronate with liposomes formed from synthetic phospholipid l-palmitoyl-2-oleoyl-phosphatidylcholine (POPC).

Viscosupplementation with intra-articular hyaluronic acid (HA) is routinely used in clinical practice for the management of osteoarthritis (OA) and joint diseases. The novelty of this device resides in the addition of POPC to HA for intra-articular injections.

The device is claimed as completely novel by the manufacturer and the CEAR confirms (pages 3, 10, 15) that no comparators (equivalent or similar devices) are available. The combination of HA and POPC has been previously proposed for surface wound treatment in foils, but not to be injected intraarticularly.

1.2 Possible negative clinical / health impact resulting from novelty

Estimated* possible clinical and/or health impact related to the novel aspects of the device

* This can entail uncertainty. Not only *known* clinical / health impacts but also *possible* ones (conceivable uncertainties, hazards, risks) should be taken into account but need to be supported by a scientific, clinical or technical reasoning.

☐ No clinical or health impact
☐ Minor clinical or health impact
☒ Moderate clinical or health impact
☐ Major clinical or health impact

Possible major clinical or health impact related to the novel aspects of the device

According to the manufacturer, POPC is expected to increase the stability of hyaluronic acid in the physiological environment, thus ensuring long-term maintenance of the biomechanical parameters of the synovial joint. POPC is also expected to improve the lubrication effect of HA, influencing the restoration of optimal rheological and tribological parameters of the synovial fluid, which improves joint mobility and reduces pain.

There is a possible moderate clinical/health impact related to the addition of POPC to HA. While the combination of HA and POPC may provide an interesting benefit, this combination lacks clinical assessment. One of the possible risks is the possibility of aggregates formation in the joint after injection, thus affecting the joint function.

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**

2.1 Information received from Secretariat:	☐ Yes ☒ No
2.2 Other information available to experts:	☐ Yes ☒ No

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

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 OF THE THEMATIC EXPERT PANEL/SUB-GROUP

2.1 Information on panel and sub-group

Date of opinion	07/04/2025
Expert panel name	Orthopaedics, traumatology, rehabilitation, rheumatology
Sub-group of expert panel (where relevant)	Non-articulating devices and rehabilitation

2.2 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 manufacturer's clinical evaluation report
In general, the CEAR lacks detail on the critical assessment performed by the NB while reviewing the clinical data presented by the manufacturer of the device. Due to the novelty aspects associated with the device, the manufacturer excluded the possibility of using clinical data generated from other clinical studies using equivalent devices and opted instead for conducting a clinical investigation. The clinical development included a prospective, open-label clinical study to assess the safety and clinical performance of the device in knee osteoarticular (OA) patients. However, it is the opinion of this expert panel that the proposed clinical study is not conclusive for the determination of the safety and clinical performance of this device and a randomised controlled study should be performed to address those uncertainties. Due to the novelty, it is also considered that a follow-up of 6 months is not sufficient to establish efficacy or safety of this device.
2. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination
For the assessment of the safety and clinical performance of the device to be used in knee osteoarticular (OA) patients to reduce pain and improve mobility, the manufacturer conducted a prospective, open-label clinical study. The assessment used patient reported outcome measures as endpoints (VAS, Western Ontario and McMaster Universities Osteoarthritis Index), three functional tests (the Timed Up and Go Test, the 5 Times Sit to Stand Test and the 10 m Walk Test) and Maximal Isometric Voluntary Contraction. The

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

panel agrees with the choice of endpoints for the objectives of a clinical study investigating safety and clinical performance in this clinical context.

However, and considering that the assessment of knee osteoarthritis pain is one of the main objectives of the study and that is measured using a patient reported outcome measure (PROM), the correct isolation of the placebo effect is of the essence[2]. For this reason, it is the opinion of this expert panel that the proposed open label clinical trial is not conclusive for the determination of the safety and clinical performance of the device, as the study was not blinded for patients or investigators, there was no control group and the main outcome variables are subjective (high-risk of assessment bias).

In summary, the panel disagrees with the choice of clinical study design to assess the benefit-risk and considers that only a randomised controlled study is adequate to correctly demonstrate the clinical benefits attributed to the device, something that is commonly used for these indications[3].

The literature review is also of limited adequacy, with 10 of the 17 references being older than 10 years, some even older than 20 years.

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

Lipotris is recommended for pain and decreased articular mobility associated with traumatic or degenerative changes including osteoarthritis. Because the assessment of pain is very subjective and highly affected by the placebo effect (as mentioned before), a randomised controlled study (RCT) is necessary for the isolation of the treatment effect by comparing outcomes between the treatment and control groups.

The primary outcome should focus on pain intensity, often measured using standardised scales like the Visual Analog Scale (VAS) or the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale. Secondary outcomes might include functional improvement, assessed through tools like the WOMAC function subscale or the Knee Injury and Osteoarthritis Outcome Score (KOOS).

4. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the PMCF plan

The proposed PMCF plan is to be applicable to all similar products produced by the manufacturer of Lipotris. However, Lipotris is defined by its manufacturer as being a novel product by adding liposomal POPC to the more conventional devices used for viscossupplementation that use hyaluronic acid only.

Although the panel has no specific recommendations, the manufacturer should assess critically if there are any gaps of information regarding the novelty aspects and how these can impact the safety and performance of this device, including the clinical benefit, throughout its expected lifetime.

[2] Zhang W. The powerful placebo effect in osteoarthritis. Clin Exp Rheumatol. 2019 Sep-Oct;37 Suppl 120(5):118-123. Epub 2019 Oct 15. PMID: 31621561.

[3] Pereira TV, Jüni P, Saadat P, et al. Viscosupplementation for knee osteoarthritis: systematic review and meta-analysis. BMJ. 2022 Jul 6;378:e069722. doi: 10.1136/bmj-2022-069722. PMID: 36333100; PMCID: PMC9258606.

Additionally, the panel also considers that a follow-up of 6 months is not sufficient to establish completely establish the efficacy or safety, and recommends that a 1 to 2 years of follow-up is conducted instead.

2.3 Summary of expert panel opinion

Lipotris is a viscoelastic gel composed of native sodium hyaluronate (HA) with the addition of liposomes formed from l-palmitoyl-2-oleoyl-phosphatidylcholine (POPC) of synthetic, non-animal origin. The addition of POPC in Lipotris is intended to increase the stability of hyaluronic acid in the physiological environment and to support long-term maintenance of the synovial joint biomechanical parameters.

The intended purpose of Lipotris is intraarticular joint viscosupplementation in patients with developed pain and decreased articular mobility associated with traumatic or degenerative lesions of the knee and other synovial joints, including osteoarthritis. It is designed to be injected into the knee or other synovial joints to relieve pain and increase articular mobility.

Lipotris is a synovial fluid substitute destined to promote the restoration of rheological conditions of the joints (knee or other synovial joints) altered by degenerative or post-traumatic conditions. The product should improve the characteristics of the synovial fluid, exert a protective action on the joints, and help improve joint function and reduce pain symptoms. The effects of the treatment are claimed to last at least 6 months.

The panel considers that the evidence presented cannot adequately establish the safety and clinical performance of this device, mostly due to the impact that the placebo effect has on pain assessment using a PROM. For this reason, a randomised controlled design is suggested as an alternative possibility to generate evidence.

2.4 Recommendations

The NB should require the manufacturer to conduct an RCT and include a period of follow-up of at least 1 to 2 years to establish in a robust way the safety and clinical performance of this device.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[4]
Has the Secretariat provided information from stakeholders?
☐ Yes ☒ No
Summary of the information that was taken into account and how it was taken into account.

[4] 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.

N/A

2.6 Divergent positions in case no consensus was reached

Please indicate how many of the experts of the panel or sub-group had divergent views
N/A
Summary of divergent positions
N/A