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 start of procedure	11/03/2025
Notified Body number	NB0123
Internal CECP dossier #	EMA/EX/0000256552
Medical device type	Female contraceptive
Intended purpose	Intended for non-surgical permanent birth control by occlusion of the fallopian tubes.
Risk class / type	☒ class III implantable ☐ class IIb active device intended to administer or remove medicinal products(s)
Screening step: medical field / competence area	Obstetrics and gynaecology, including reproductive medicine

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	24/03/2025
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)	
NA	
Summary as to why there is intention to provide an opinion	
A novel intrauterine device that includes integrated uterine cornua and tubal occluders represents an innovation in contraceptive technology. Unlike conventional intrauterine devices that act locally within the uterine cavity, this device combines intrauterine and tubal-level contraception in a single system, directly targeting both fertilization and implantation pathways. Due to its novelty and potential major clinical impact regarding reproductive health, safety, and reversibility an expert panel opinion needs to be provided.	
Any other comments	
NA	

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 novelty lies not in the principal of tubal occlusion per se, but in the method of occlusion, specifically the non-surgical, in-office approach and the use of a polymer-based closure via an intrauterine system. This mechanism is fundamentally different from surgical ligation and represents a new approach. Furthermore, the blended polymer is claimed to degrade and leave the body, so the

device is also different from other contraceptive methods that remain inside the uterus. Thus, neither the effectiveness nor the specific risks can be derived and compared.
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
The possible clinical or health impact of the novel aspects of the device is high, as its primary function is permanent contraception. A failure in effectiveness, due to incomplete tubal occlusion or device malfunction, could result in an unintended pregnancy. This would have significant physical, psychological, and social consequences for the individual, particularly in the context of a device intended to eliminate the probability of conception. Therefore, the reliability of the novel occlusion mechanism is of critical importance.

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

2 SCIENTIFIC OPINION OF THE THEMATIC EXPERT PANEL/SUB-GROUP

2.1 Information on panel and sub-group

Date of opinion	08/05/2025
Expert panel name	Obstetrics and gynaecology, including reproductive medicine
Sub-group of expert panel (where relevant)	NA

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
FemBloc Permanent Birth Control ("FemBloc"), is a female permanent birth control option that claims a non-surgical, office-based option for permanent contraception via occlusion of the fallopian tubes followed by an ultrasound-based confirmation test. FemBloc is comprised of the delivery system and the blended polymer in a cartridge that is inserted into the system. According to the manufacturer, the FemBloc delivery system facilitates the accurate delivery of the FemBloc blended polymer, a synthetic pre-mixed blend of cyanoacrylate-based tissue adhesive designed for use with the FemBloc delivery system, into each uterine cavity cornu and fallopian tubes. Upon delivery and contact with biological tissue and tubal fluid, the blended polymer adhesive begins to polymerize. The blended polymer is intended to induce irritation and, through a wound healing response, form nonfunctional scar tissue while the polymer degrades and exits the body through the vagina. Three months post the FemBloc procedure, a confirmation test (ultrasound Sono-HSG) is performed to assess for bilateral tubal occlusion and upon confirmation the woman can rely on FemBloc for permanent contraception. Overall, the NB provided in the CEAR a systematic assessment of the manufacturer's clinical evaluation. Given that the clinical evidence base for the device included several clinical studies, the CEAR would benefit from a more detailed discussion on the particularities and the results of each clinical study separately. Instead, the NB followed in their assessment the manufacturer approach in the clinical evaluation report as detailed in the following sections. Additionally, the expert panel raises several issues about the content and the outcome of the assessment as detailed below.
2. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination
The clinical evidence base for the device under evaluation (DUE) consists of 3 completed/ terminated clinical studies, the BLOC studies (CP-100-006, CP-100-007, CP-100-008) and the ongoing FINALE study (CP-100-009). Study CP-100-006 was a pilot study with a primary safety objective. Study CP-100-007 was a pivotal prospective controlled, non-randomised, two-arm trial with a laparoscopic

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

bilateral tubal sterilisation control arm. Study CP-100-007 was paused due to higher-than-expected number of pregnancies (6 in study CP-100-006, 3 in study CP-100-007). Confirmation tests for these pregnancies were adjudicated by an independent clinical events committee, and it was determined that all were due to misinterpretation of the confirmation test. Following that, the manufacturer completed study CP-100-008 to demonstrate improvements to the confirmation test and the relevant investigator training. The ongoing FINALE study is a pivotal study that has recently started recruiting. It is a prospective, single arm trial aiming to recruit up to 573 women with a primary endpoint of confirmed pregnancy rate at 1 year in women that were told to rely on the DUE for birth control. Importantly, the FINALE study is designed to have two applications of FemBloc followed by one confirmation test. This is in contrast to the BLOC studies in which there was one application of FemBloc followed by the confirmation test. In the context of the clinical evaluation and the NB assessment, the FINALE study is assessed as a PMCF study.

Results from individual studies are not the focus of the clinical evaluation or the NB assessment. Instead, the clinical evaluation is based on a post-hoc analysis of a cohort of 229 women that participated in the BLOC studies. Due to concerns with unintended pregnancies (n=9) among the first 117 cases, 67 women underwent the confirmation test but were not permitted to receive a result and were followed up for safety only. Additionally, adjudication of trial eligibility and product specification analysis resulted in further exclusions and in only 101 subjects who met the trial requirements and received a confirmation test result. Pregnancy rate effectiveness was analysed for the 51 of the remaining 101 women who were determined bilaterally occluded by the investigator. 228 participants who completed the FemBloc procedure were assessed for safety over a period of 5 years.

The NB found the manufacturer‘s benefit-risk determination adequate based primarily on the above post-hoc analysis derived from the BLOC studies. The adverse events reported during those trials were spotting and cramps. They were classified as mild and resolved no longer than a few days after the procedure. At the confirmation test 90 days post procedure, there were no reports of cervical scarring, hematuria, or intrauterine adhesions. At the 5 years follow-up timepoint there were no reports of ectopic pregnancy or uterine perforation.

The expert panel notes some apparent inconsistencies in the CER that should be further assessed. For example, in the safety parameters an incidence of not more than 30% of mild adverse events like cramping or spotting are expected, while in the reported safety data from the BLOC study derived cohort it appears that close to 60% of participants had vaginal spotting/bleeding or pelvic pain/ cramps. The expert panel also notes that patient reported outcomes were not sufficiently reported in the CER.

The expert panel notes that the CER appears to include literature regarding the DUE and tubal ligation. Previous tubal occlusion devices (e.g. Essure, Adiana) were excluded from the search. However, these devices generated relevant data concerning tubal occlusion. This should be considered by the manufacturer in the clinical evaluation, despite the devices not being available currently.

The expert panel also raises additional concerns and issues that may require a more in-depth assessment on the implications or additional considerations for patients with endometriosis as well as for women with irregular or absent menstrual cycles (e.g. women with polycystic ovary syndrome). There is inadequate detail on the assessment of the evidence base of polymer clearance. Additionally, an assessment of the potential failure of the blended polymer to adhere to the intended site or polymer migration will need to be addressed.

Additionally, it is noted that occlusion is achieved by means of a cyanoacrylate-based tissue adhesive. This is intended to provide a 'natural inflammatory response' as mentioned in the CER. The manufacturer claims that testing for biocompatibility has been undertaken. The manufacturer states that there have been historical applications of cyanoacrylates with no safety issues reported, however there are no citations for this claim. This was also excluded from the literature search as the search only focused on FemBloc and surgical ligation. The manufacturer also claims that toxicity can be expected to be low as these materials are used within other devices such as cardiovascular or neurological devices. This is significantly different to a material which is implanted for a contraceptive purpose. Further details on the evidence base for these claims should be provided.

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

As mentioned in the previous section, the evidence base for the effectiveness of the device in terms of pregnancy rates is based primarily on a post-hoc analysis of a cohort of 229 women derived from the three BLOC studies. Whereas for safety all participants that received the device were analysed, for effectiveness this was not the case. Due to concerns with unintended pregnancies (n=9) among the first 117 cases, 67 women underwent the confirmation test but were not permitted to receive a result and were followed up for safety only. Additionally, adjudication of trial eligibility and product specification analysis resulted in further exclusions and in only 101 participants who met the trial requirements and received a confirmation test result. Pregnancy rate effectiveness was analysed for the 51 of the remaining 101 women who were determined bilaterally occluded by the investigator.

The expert panel expresses concerns about the evidence base supporting the claim of the zero-pregnancy rate. Overall, in the CER it is mentioned that there were 9 pregnancies in the BLOC studies. The claim of the zero-pregnancy rate is based on a post-hoc analysis of a group of participants in the BLOC studies after exclusion of more than three quarters of the overall cohort, including the women that had unintended pregnancies. The reasons for these exclusions are not adequately reported in the CER. While useful for exploratory purposes, the provided evidence is not suitable as conclusive evidence of effectiveness of the DUE. The FINALE study has recently started recruitment and the cited numbers (13 women have completed a confirmation test, follow-up not mentioned) are not adequate for any conclusions to be drawn.

Irrespective of the concerns mentioned above regarding the high risk of bias of the provided analysis, the expert panel notes that a sample size of 51 women followed up for a year is not adequate to confirm a pregnancy rate of less than the cited performance goal in the CER. For example, the FINALE study requires that 573 participants are enrolled in order to have a 90% chance of demonstrating at the one-sided 0.05 significance level that the one year confirmed pregnancy rate is less than 6%, assuming that the true rate of pregnancy for those told to rely on FemBloc is 3% and assuming an overall attrition rate of up to 30%.

Additionally, it is noted that in the post-hoc analysis from the BLOC studies only 51 women were determined to be bilaterally occluded after the confirmation test out of the 101 women who met the trial requirements and received a confirmation test result. This raises concerns about the percentage of women that were told to rely on the device for contraception after application of the device, although it is difficult to derive an exact percentage given the post-hoc nature of the analysis and the large number of excluded participants. The resulting clinical implications have not been assessed adequately. It is unclear, based on the available evidence, what is the percentage of women that receives the device and can rely on the device for contraception. It is noted that in the FINALE study two applications of the device are required before the confirmation test.

The expert panel also notes that while in the BLOC studies the age of the participants was 21-45 years, the device is intended to be used in women between 21-50 years of age. It is understood that

this evidence gap is expected to be addressed in the PMCF, given that the FINALE study allows recruitment of participants between 21-50 years.

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

The PMCF plan is overall comprehensive. In addition to general PMCF activities, the manufacturer is including an ongoing prospective, multi-center, unblinded, single-arm trial of women undergoing FemBloc titled FINALE to evaluate the safety and effectiveness of the device in preventing pregnancy as a PMCF study. It is planned to enrol 573 participants at up to 25 sites in the USA and internationally. The trial schedule is approximately 6 years, which includes a 3-month waiting period after the second FemBloc application followed by a confirmation test and a subsequent 5-year follow-up period while relying on FemBloc. The intervention overall consists of 2 applications of FemBloc followed by 1 confirmation test.

The expert panel notes the difference between the BLOC studies in which there was one application of FemBloc followed by a confirmation test and the FINALE study. It is understood that the device is intended to be applied once followed by a confirmation test and a second application is only allowed in cases in which the confirmation test does not demonstrate bilateral occlusion. It is unclear in the provided documentation what is the reason that a different procedure is used in the FINALE study. The expert panel is concerned that the FINALE study will not be suitable to address evidence gaps that were identified in previous sections, for example the percentage of women that can rely on Fembloc for permanent contraception after one application of the device.

Additionally, given that this is a permanent contraceptive device, extension of follow-up should be considered as well as potentially collecting data in younger ages in PMCF. Relevant data from annual progress reports for studies ongoing in the US should be analysed and evaluated in the CER in detail.

2.3 Summary of expert panel opinion

The DUE is a female permanent birth control option that claims a non-surgical, office-based option for permanent contraception via occlusion of the fallopian tubes followed by an ultrasound-based confirmation test.

The NB assessment of the manufacturer's clinical evaluation is overall systematic and comprehensive.

However, the expert panel raised several issues as detailed in the previous sections including:

- High risk of bias in the provided post-hoc pregnancy rate effectiveness analysis in a cohort of 51 patients derived from 3 completed/ terminated studies (BLOC studies). Several concerns arise regarding the evidence base, cohort size, and generalizability of the clinical data.
- The size of the cohort that was evaluated in the CER is not sufficient to provide conclusive evidence on pregnancy rates.
- No conclusive data on the percentage of women that have the procedure and can rely on that for contraception are presented.
- Issues are raised regarding the evidence base supporting the safety of the device and specific patient populations.
- Regarding the proposed PMCF study, the FINALE trial, the expert panel is concerned it will not be suitable to address evidence gaps that were identified in previous sections, for example the percentage of women that can rely on Fembloc for permanent contraception after one application of the device.

2.4 Recommendations

The expert panel has the following recommendations based on the review of the submitted documentation:

- Adequate reporting of individual BLOC studies should be provided in the CER.
- Any attempt for evidence synthesis on pregnancy rates should acknowledge and manage the risk of bias, for example lack of prespecification, differences in interventions including the confirmation tests.
- Reporting should be transparent for the whole intention to treat population.
- Additional premarket data on the safety and performance of the device should be gathered by the manufacturer and assessed by the NB.
- If the majority of the data required to provide conclusive premarket evidence comes from the FINALE study, the clinical use of the device is expected to reflect the use of the device in that study, i.e. two applications of the device and then the confirmation test.
- Longer follow-up data are needed in terms of safety and clinical performance.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[2]
Has the Secretariat provided information from stakeholders?
☒ Yes ☒ No

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
Zero

[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.