



Expert decision and opinion in the context of the Clinical Evaluation Consultation Procedure (CECP)

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

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Scope of this expert decision

This decision reflects the views of independent experts (MDR Article 106) on the relevance to produce an opinion on the clinical evaluation assessment report (CEAR) of the notified body for this device. The expert decision 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).

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 notified 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 start of procedure	13/03/2026
Notified Body number	NB 2797
Internal CECF dossier #	EMA/EX/0000336395
Medical device type	Z1204: General medicine instruments
Intended purpose	Disposable Cervical Photodynamic Therapy Lamp (CEVIRA device, Model CL7) is intended to be used in combination with the CEVIRA (hexaminolevulinate hydrochloride, HAL·HCl) ointment to administer the ointment transvaginally to the cervix and emit red light to activate the ointment, thereby inducing a photodynamic therapy effect for the treatment of adult women (≥ 18 years) with histologically confirmed cervical high-grade squamous intraepithelial lesions corresponding to cervical intraepithelial neoplasia grades 2 and 3.
Risk class / type	Class IIb
Screening step: medical field / competence area	Obstetrics and gynaecology, including reproductive medicine

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	01/04/2026
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	
Photodynamic therapy (PDT) represents a clinically established technology in other medical fields, offering potential advantages regarding traditional surgical methods, including tissue preservation and potential effects on viral persistence. However, this is a novel approach in the specific context of histologically confirmed high grade squamous intraepithelial lesions (HSIL) of the cervix uteri. Considering the initial uncertainties regarding the benefit–risk balance and the alignment of the clinical evidence with the intended medical indication, a scientific opinion is necessary.	
Summary as to why there is <u>no</u> 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

PDT is an established technology in other medical fields (most notably in dermatology), however its application in cervical dysplasia represents a novel therapeutic use in the clinical context of cervical HSIL.

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

As a destructive treatment modality, PDT does not provide tissue for histopathological evaluation. In the context of cervical HSIL, this limitation may restrict the ability to reliably exclude occult invasive disease. According to European clinical guidance on the management of cervical precancerous lesions, excisional procedures are recommended in order to allow comprehensive histopathological assessment. Consequently, the use of a purely destructive approach may affect diagnostic certainty and patient safety within cervical cancer prevention programs. With this consideration, the impact of the use of this technology can be major.

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 the secretariat	☐ Yes ☒ No
2.2 Other information available to the experts	☐ Yes ☒ No

Criterion 3: Significant increase of serious incidents of a specific group / category of devices relevant for the device under assessment <i>(if information is available, it will always be provided by the expert panel secretariat)</i>	
3.1 Information received from the 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 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
☐	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	12/05/2026
Expert panel name	Obstetrics and gynaecology, including reproductive medicine
Sub-group of expert panel (where relevant)	N.A.

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 (CER)
The expert panel reviewed the CEAR and the CER, and the clarifications provided during the discussion meeting with the NB. The CEAR demonstrates a structured and comprehensive assessment of the submitted clinical evidence. Initial concerns relating to the implications of a destructive treatment modality were further clarified during the experts' discussions, in particular with regard to strict inclusion and exclusion criteria, central pathology review, and explicit exclusion of patients at higher risk of invasive disease. Following these clarifications, the panel considers that the CEAR provides a generally adequate and scientifically reasoned assessment of the manufacturer's clinical evaluation for the defined intended population. The panel notes that, because the pivotal study was conducted using highly standardised diagnostic procedures, its findings are applicable to European clinical practice only when the device is used under similarly strict and well-controlled conditions, which limits generalisability to a broader patient population.
2. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination

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

The clinical performance and safety of the CEVIRA device, used in combination with the CEVIRA ointment, were evaluated primarily in the pivotal phase III clinical investigation YHGT-CEV-R1. This study was designed to assess the efficacy and safety of photodynamic therapy (PDT) as a non-excisional treatment for cervical high-grade squamous intraepithelial lesions (HSIL) grades 2 and 3 of the Cervical Intraepithelial Neoplasia (CIN) histological grading system.

Study Design

YHGT-CEV-R1 was a prospective, randomised, double-blind, placebo-controlled, multicentre clinical investigation conducted across multiple sites in China and Europe. Eligible participants were randomised in a 2:1 ratio to receive either:

- CEVIRA treatment (CEVIRA ointment with active PDT lamp), or
- Placebo control (placebo ointment with visually identical, inactive lamp).

The study was conducted under double-blind conditions, with patients, investigators, outcome assessors, and pathologists blinded to the assigned intervention.

The study design incorporated independent central pathology review and predefined criteria for lesion characteristics to ensure homogeneity of the study population and reliability of the outcome assessment.

Study Population

Adult women with biopsy-confirmed cervical HSIL (CIN2/3) were enrolled. Key eligibility criteria included:

- Histologic confirmation of HSIL by central expert pathology review
- Lesions fully visible on colposcopy
- Lesion size and cervical anatomy compatible with correct device placement
- Absence of invasive disease or endocervical canal involvement

A total of 402 subjects were randomised, of whom 382 subjects constituted the modified intention-to-treat (mITT) population after central pathology confirmation. 20 subjects were excluded from the ITT dataset after central review because their histology did not confirm CIN2/3, or they failed another critical eligibility criterion confirmed centrally.

Intervention and Follow-up

Participants received one treatment with the CEVIRA device; a second treatment was allowed if the predefined response criteria were not met. The device was inserted by trained gynaecologists and delivered controlled light activation following application of CEVIRA ointment, with the device remaining in situ for a period of approximately 9 hours per treatment session.

Subjects were followed for 6 months for the primary endpoint assessment, with extended follow-up to 12 months for evaluation of response durability and safety.

Primary Outcome Measure

The primary clinical efficacy outcome measure was the proportion of responders at 6 months post-treatment, defined as either:

- Normal cervical histology, irrespective of HPV status or
- Low-grade squamous intraepithelial lesions (LSIL) histology combined with clearance of the HPV infection present at baseline.

This composite endpoint was selected to reflect both histologic improvement and virologic outcome.

Clinical Performance Results

At the 6-month assessment:

- 41.1% of subjects treated with CEVIRA met the responder definition, compared with 21.7% in the placebo group.

The difference between treatment groups was considered to be statistically significant. Treatment effects were observed consistently across relevant subgroups, including CIN2 and CIN3 lesions, HPV genotype categories, and geographic regions.

Secondary efficacy endpoints, including histologic regression independent of HPV status, HPV clearance rates - particularly for high-risk genotypes - and other indicators of lesion regression support biological plausibility of primary confirmatory claims.

Follow-up to 12 months showed that treatment responses were generally sustained over time, with some patients showing continued improvement beyond the initial evaluation period, supporting durability of the treatment effect.

Safety Outcomes

Safety was assessed through the recording of adverse events, device incidents, and pregnancy outcomes. The overall incidence of treatment-emergent adverse events was comparable between the active and placebo groups.

Most device-related or treatment-related adverse events were local, mild to moderate in severity, and transient. Commonly reported events included vaginal discharge, mild pelvic pain, and vaginal bleeding, consistent with the known effects of PDT and intravaginal device use. Serious adverse events were rare and primarily consisted of isolated pregnancy-related events and unrelated medical conditions, with no device-related serious safety concerns identified.

The expert panel acknowledges that PDT is a non-excisional treatment modality and therefore does not provide histopathological specimens. This aspect raised initial concerns regarding diagnostic certainty in HSIL management. However, during the discussion meeting with the NB it was clarified that exclusion of extensive CIN3 lesions and suspected invasive disease, together with robust diagnostic confirmation (including central pathology review and adequate colposcopy), is part of the patient selection.

Based on the available short-term clinical data, the benefit-risk determination in the evaluated patient group appears acceptable. This conclusion is supported by demonstrated clinical benefit

versus placebo for the primary efficacy endpoint, a generally favourable safety profile, and indications of potential advantages with respect to cervical tissue preservation and reproductive health.

From a device's perspective, the expert panel notes that usability-related aspects, including correct insertion, device retention, and removal, were addressed in the clinical investigation and did not raise significant safety concerns. Reported device-related events were infrequent and predominantly mild, supporting the usability of the device within the defined clinical setting.

The expert panel further notes that no clinically relevant concerns related to device malfunction, premature cessation of light delivery, or failure to deliver the intended therapeutic dose were identified in the evaluated clinical evidence.

Notwithstanding these favourable short-term findings, the current clinical evidence does not yet adequately address residual oncological risk, including the possibility of undetected invasive disease at baseline and the lack of direct comparative evidence versus excisional management strategies. These gaps represent important limitations when considering a comprehensive and robust benefit-risk determination in this clinical setting.

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

The intended purpose of the device is to be used in combination with the CEVIRA ointment to administer the ointment transvaginally to the cervix and to emit red light for activation of the ointment, thereby inducing a PDT effect for the treatment of adult women with histologically confirmed cervical HSIL (CIN2/3).

The panel notes that, while excisional procedures remain the standard of care in European clinical guidelines, conservative and fertility-preserving treatment approaches are increasingly recognised for selected patient populations under specific clinical conditions.

During the discussion meeting with the NB, it was clarified that the clinical evidence, together with the defined inclusion criteria, warnings, and contraindications, collectively limits the use of the device to a narrowly defined subgroup of patients with HSIL. In particular, patients with extensive CIN3 disease or other conditions associated with increased oncological risk are excluded.

Taking these constraints into account and based on the explanations provided by the NB, the expert panel acknowledges that the use of the device may, in principle, be considered for selected patient subgroups within a clearly defined and controlled clinical setting. However, the panel considers that these subgroups are not yet sufficiently and unambiguously characterised in the clinical evidence assessed within the CEAR. Furthermore, such use must be interpreted in the context of current international clinical guidelines and established standards of care.

Consequently, the panel concludes that the available clinical evidence is insufficient to support an unrestricted positive conclusion regarding consistency with the stated intended purpose.

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

During the discussion meeting with the NB, the absence of a formal interventional Post-Market Clinical Follow-Up (PMCF) study was discussed. The NB explained that the device is intended for local, short-term use, employs a well-established photosensitiser with a favourable safety profile, and incorporates clearly defined contraindications that restrict its use in higher-risk patient populations.

Notwithstanding these considerations, the panel notes that the proposed PMCF framework does not clearly define how key long-term safety aspects, including oncological outcomes and reproductive safety, will be prospectively and systematically monitored in order to address the residual uncertainties identified.

Accordingly, while the proposed PMCF approach includes elements such as systematic post-market surveillance, targeted user feedback, literature review, and vigilance activities, the panel considers that it is not clear whether these measures are adequate to address the clinically relevant long-term safety concerns.

In the panel's view, further strengthening of the PMCF strategy is recommended, for example through the inclusion of structured, prospective data collection mechanisms of sufficient duration to capture long-term oncological outcomes and reproductive events following device use. Such an enhanced PMCF approach should be capable of generating clinical outcomes relevant to guideline-based management, including oncological safety and clinically relevant consequences of a non-excisional approach, in order to substantiate the benefit-risk profile of the device in relation to established excisional treatment options in the intended patient population.

2.3 Summary of expert panel opinion

The assessment of the suitability of the device must be made in relation to international consensus recommendations and established best practice. In this context, and as was stated again during the expert discussion, the submitted data would need to allow an adequate comparison between excisional treatment and a destructive procedure. Such a comparison is necessary in order to appropriately assess the benefit-risk profile, particularly given the absence of histopathological specimen retrieval after device use.

The panel therefore considers that the intended patient population, the conditions of use, and the relationship of the device to established guideline-based management should be described in a more precise and differentiated manner. This is necessary to provide adequate clarity for both users and patients regarding the clinical situations in which use of the device may be appropriate.

Accordingly, while the discussion with the NB clarified that the device may be used in a restricted subpopulation, further clarification and refinement are necessary before a positive benefit-risk conclusion can be supported.

In the panel's view, addressing these limitations would require additional data generation, proportionate to the identified residual risks, to enable a more robust positioning of the device within the established standard of care.

2.4 Recommendations

The expert panel recommends the following actions to the NB:

1. Ensure that the approved intended purpose, indications, contraindications, and warnings accurately reflect the restricted patient population evaluated in the clinical investigation.
2. Verify that the instructions for use clearly emphasise the non-excisional nature of the treatment and the requirement for appropriate diagnostic work-up, including exclusion of higher-risk disease prior to use.
3. Maintain and further strengthen post-market surveillance and PMCF activities, with particular focus on the prospective and systematic capture of oncological outcomes, including disease progression or delayed diagnosis of invasive disease, as well as reproductive outcomes, supported where appropriate by structured data collection mechanisms.
4. Require periodic reassessment of the benefit-risk profile as additional post-market and real-world data become available.

During the discussion with the NB, the panel further noted that the available clinical evidence supports use of the device within a narrower clinical context than originally described. The panel therefore recommends that the NB consider whether the intended purpose should be refined to explicitly reflect use as a non-excisional, fertility-preserving treatment option for a selected subgroup of adult women with histologically confirmed HSIL, particularly CIN2 lesions, where strict diagnostic criteria are applied and higher-risk disease - including extensive CIN3 and suspected invasive carcinoma - is excluded. Such refinement would ensure better alignment between the intended purpose, the investigated population, and current European clinical practice, while reducing the risk of use in clinical situations not supported by the available evidence.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable²

Has the secretariat provided information from stakeholders?

☐ Yes

☒ No

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.

Summary of the information that was taken into account and how it was taken into account.
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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
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No divergent views

Summary of divergent positions

N/A
