



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)

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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, adaptation 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	17/04/2023
Notified Body number	NB0477
Internal CECP dossier #	EMA/EX/0000137387
Medical device type	MALE GENITAL SYSTEM PROSTHESES
Intended purpose	Hyaluronic Acid Sodium Salt for intralesional penile injection intended for treatment of the acute phase of Peyronie's Disease.
Risk class / type	<input checked="" type="checkbox"/> class III implantable <input type="checkbox"/> class IIb active device intended to administer or remove medicinal products(s)
Screening step: medical field / competence area	Nephrology and urology

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	17/10/2023
Screening panel decision	
Is there intention to provide a scientific opinion?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> 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	
<p>The device under assessment is a new market launch, it has no CE mark, and with no device equivalent.</p> <p>The four studies that are available indicate a high uncertainty in relation to the long-term safety of the device as the available data only has 3 months follow up. The proposed posology in the claimed indication is uncertain.</p>	
Summary as to why there is <u>no</u> intention to provide an opinion	
N/A	
Any other comments	
No additional comments.	

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
<input type="checkbox"/> No novelty: Neither device nor clinical procedure is novel <input type="checkbox"/> Low level of novelty <input type="checkbox"/> Medium level of novelty <input checked="" type="checkbox"/> High level of novelty
Short description of the novelty, including main dimension(s) of novelty
<p>The device is considered as having a high degree of novelty, since it is indicated for the management of acute phase of Peyronie's Disease in contrast to previously available injectables used in stable phase of the plaque.</p> <p>Only one intrapenile treatment is on the market which is a combination of bacterial collagenases indicated for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.</p>
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
<p>* This can entail uncertainty. Not only <i>known</i> clinical / health impacts but also <i>possible</i> ones (conceivable uncertainties, hazards, risks) should be taken into account but need to be supported by scientific, clinical or technical reasoning.</p>
<input type="checkbox"/> No clinical or health impact <input type="checkbox"/> Minor clinical or health impact <input checked="" type="checkbox"/> Moderate clinical or health impact <input type="checkbox"/> Major clinical or health impact
Possible major clinical or health impact related to the novel aspects of the device
<p>Based on the available data the experts identified the following uncertainties.</p> <ul style="list-style-type: none"> • Regarding the safety of the device an uncertainty in relation to the long-term usage of the device is stemming from the limited follow up data of 3 months. • Another uncertainty is stemming from various methodological limitations of the clinical studies (e.g. lack of formal randomization versus sham control groups, lack of dose response study) • Limited information about the degradation profile of the device • Limited information about the dosing as well as the treatment period

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

	Expert panels	Medical and scientific/technical competence areas (these may correspond to sub-groups)
<input type="checkbox"/>	Orthopaedics, traumatology, rehabilitation, rheumatology	<input type="checkbox"/> 1. Joint replacements (hip, knee, shoulder) <input type="checkbox"/> 2. Spinal devices <input type="checkbox"/> 3. Non-articulating devices, rehabilitation
<input type="checkbox"/>	Circulatory system	<input type="checkbox"/> 1. Prosthetic heart valves and devices for heart valve repair <input type="checkbox"/> 2. Cardiovascular stents (metallic and bio-resorbable) and vascular prostheses <input type="checkbox"/> 3. Active implantable cardiac devices and electrophysiological devices <input type="checkbox"/> 4. Structural interventions and new devices (e.g. LAA/PFO occluders, heart failure devices) <input type="checkbox"/> 5. Cardiac surgery including extracorporeal membrane oxygenation, cardiopulmonary bypass devices, artificial hearts and left ventricular assist devices
<input type="checkbox"/>	Neurology	<input type="checkbox"/> 1. Central and peripheral nervous system devices <input type="checkbox"/> 2. Implants for hearing and vision (sensory recovery) <input type="checkbox"/> 3. Neurosurgical devices
<input type="checkbox"/>	Respiratory, anaesthesiology, intensive care	<input type="checkbox"/> Respiratory and anaesthetic devices
<input type="checkbox"/>	Endocrinology and diabetes	<input type="checkbox"/> Endocrinology and diabetes devices
<input type="checkbox"/>	General and plastic surgery Dentistry	<input type="checkbox"/> 1. Surgical implants and general surgery <input type="checkbox"/> 2. Plastic surgery and wound care <input type="checkbox"/> 3. Maxillofacial surgery & Devices for dentistry e.g. oral surgery, implantology, dental materials etc.
<input type="checkbox"/>	Obstetrics and gynaecology including reproductive medicine	<input type="checkbox"/> Devices for obstetrics and gynaecology
<input type="checkbox"/>	Gastroenterology and hepatology	<input type="checkbox"/> Devices for gastroenterology and hepatology
<input checked="" type="checkbox"/>	Nephrology and urology	<input checked="" type="checkbox"/> Devices for nephrology and urology
<input type="checkbox"/>	Ophthalmology	<input type="checkbox"/> 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	05/12/2023
Expert panel name	Nephrology and urology

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
<p>The European Association of Urology guideline on Sexual and Reproductive Health, update 2023, contains a chapter (chapter 8.2) on all aspects of Peyronie's Disease, including different conservative and surgical treatment options. Hyaluronic acid (HA) was reported in the guidelines mentioned above, among other intralesional treatments (sub-chapter 8.2.3.1.2). In the guidelines, intralesional treatment was summarized under „injection of pharmacologically active agents directly into penile plaques represents another treatment option. “</p> <p>Until now, HA and the medical device under assessment „Hyaluronic Acid Sodium Salt for intralesional penile injection" were used in several clinical studies, with the first publication in 2015, and with four publications 2016, 2017a, 2020a, and 2020b. In addition, one publication 2017b, reporting a study using a combination of HA and another agent. The total number of patients treated with HA in all studies was 417, plus 90 receiving combination therapy. Reported follow-up was 3 months in most studies, and 24 months in one study.</p> <p>All of these publications along with additional related information, e.g. from reviews and guidelines, were thoroughly reported in the CER and assessed by the NB in the CEAR. The rationale and posology of the treatment using the device, were well described.</p> <p>The panel has identified several limitations that should be considered when evaluating the available evidence: the lack of a sham control group, the short follow up, the lack of data from dose-response and risk or hazard analysis studies. In addition, there is no mid- or long-term data of the treatment over time, such as duration of the therapy and fate or the injectable, such as absorption or risk of migration.</p>

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

Although the device under assessment is a new market launch, for the indication of intralesional injection in the acute phase of Peyronie's disease, the main component (hyaluronic acid) is an agent, which is not new, and its long-term use is well-known for various medical and cosmetical applications.

Taking into account the natural course of Peyronie's disease, and the resulting consequence of limited time to treat, e.g., with intralesional injection, during the acute phase, the limited long-term data should be addressed. Specifically, the degradation profile and the possible migration of the device.

2. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination

Results in regard to the safety of the device are discussed in the documents provided. Potential safety concerns are addressed in the CER and reflected on the NB's assessment. No concerns were raised in the NB's assessment.

The leaflet of the device includes a warning on not to inject intravascularly. This leads to the question, if the involuntary intracavernosal and/or intravascular injection of HA, respectively, were investigated by the manufacturer and what were the consequences of such involuntary intravascular injection. The lesions to be treated with the injection of the device are located in the tunica albuginea, a thick covering of the corpora cavernosa, hence there is a potential risk for inadvertently intracavernosal injection. The background for the warning is not further mentioned and should be addressed in the benefit-risk determination.

Additionally, and as mentioned above, uncertainties regarding the mid and long-term possibility of migration of the device are not adequately discussed and reported. This should also be addressed in the benefit – risk assessment.

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

In total, 6 studies are available investigating the intralesional injection of hyaluronic acid in the acute phase of Peyronie's disease. One study used hyaluronic acid, not the device. This study compared 83 treated patients with 81 untreated patients, not randomized. However, to a certain extent it allows to compare HA injection with the natural course of the disease. Treatment was done for a period of 6 months; the follow-up was 24 months. One study without comparator used a combination of HA and another agent. This study cannot be included to demonstrate the performance of HA on the disease but could add safety data (n=90).

In four studies, named pivotal studies by the device manufacturer, likely the device was used (although not specifically mentioned in the methods), in a total 334 patients were included in these studies. One study was randomized against off-label-used verapamil (n=63 vs n=69), one study was randomized against HA plus oral HA (n=40 vs. n=41), one study compared HA and off-label-used verapamil (n=125 vs n=119), and in one study n=65 patients were treated with HA without comparator group of patients. In the pivotal studies, treatment follow-up was 3 months. Major side effects and complications of the treatment using the device were not reported. The effects on disease improvement are reported in detail in the CER.

According to the clinical studies performed and the information is presented in the CER, the intended purpose of using this device, is strictly limited to the acute phase of Peyronie's disease. To date, there is no clinical evidence available to recommend the use of this device or even HA respectively, in the chronic phase of Peyronie's disease with clinical manifestation of fibrotic and/or calcified plaques.

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

The PMCF plan includes several activities including, screening of the latest literature on the device and similar devices, feedback from users of the device as well as questionnaires. In addition, a prospective, multicentric, single arm, open-label post-market study is planned by the manufacturer. The PMCF plan is consistent with the evidence provided by the manufacturer and adequately assessed by the NB.

A longer follow up time for the proposed post market clinical study of 12 or 24 months is desirable to ensure the proper assessment of the mid and long-term effects of the treatment. In addition, considering several uncertainties in relation to the proposed study e.g. the possibility of insufficient patient recruitment the expert panel would recommend the manufacture to initiate a prospective multicentre registry study on patients treated and patients who were offered treatment but were not treated (real life data) with at least 12 months follow-up.

2.3 Summary of expert panel opinion

The device under assessment is designed to treat Peyronie's disease in its acute phase, which is the beginning and clinical manifestation of symptoms, before the disease results in a chronic manifestation of so-called plaques on and within the tunica albuginea of the corpora cavernosa. This disease is not rare. However, its cause is unknown, and no standard treatment is available. The disease leads to penile curvature, erectile dysfunction, pain, and resulting impairment of quality-of-life. Up to date, there is no available therapeutic option of the management of the early stage (acute phase) of the disease. The lack of treatment option often causes frustration to patients, since the acute phase is related with pain, disease progression, marked deterioration of curvature, and often sexual dysfunction.

The device under assessment is a gel, containing as the main component hyaluronic acid sodium salt. This gel is administered by intralesional injection. The physical characteristics of HA make it a hydrophilic agent. HA is considered highly polarized and maintains hydration, turgor, plasticity, and viscosity in the amorphous connective tissue matrix. Additional pharmacological effects of HA could be antioxidant effects which lead to a reduction of plaque related symptoms and its antifibrotic effects which limited plaque growth.

Overall opinion of the Notified Bodies assessment: The overall opinion of the NB reflects the CER submitted by the manufacturer, including a thorough description of the disease and clinical problems, the current treatment options, and the rationale, why the device under assessment was considered to be effective and safe in the treatment of the acute phase of Peyronie's disease. The CER also includes a full report of the clinical studies being performed until now. Additional information about the long-term use of the device should be provided, including the degradation profile of the device as this is currently unknown.

Adequacy of benefit-risk determination: In this panel's opinion, the novelty and some associated risks were not addressed adequately. Particularly relevant is the fact that no information is given in the CER on what will happen with the device after it is injected and the potential risks this entails. This is particularly important because there is no long-term data from the pivotal studies, and all studies had a follow-up terminated shortly after the end of treatment. Secondly, the warning mentioned by the manufacturer on not to inject the device intravascular was not addressed adequately. Regarding the proximity of the cavernosal tissues and of blood vessels to the lesion to be treated, involuntary intravasal injection of the device is not unlikely. Risk management in the case of such an event should be included.

Consistency of clinical evidence with purpose / medical indication(s): The evidence documented in medical literature is consistent with the intended purpose of the device, which is "intralesional injection in the acute phase of Peyronie's disease", exclusively. All patient treatments reported in the studies, so far, received treatment with this indication. According to published studies, no patients were treated in the chronic phase of Peyronie's disease. It must be noted that the European Association of Urology Guidelines on Sexual and Reproductive Health, Limited Update 2023, concluded the summary of evidence with conflicting statements: „No robust evidence is available to support treatment with intralesional hyaluronic acid ...“(Level of Evidence 3c); „Intralesional hyaluronic acid may be used to improve pain, penile curvature and IIEF scores“ (Level of Evidence 2b).

Consistency of clinical evidence with PMCF plan: The manufacturer plans a prospective, multicentric, single arm, open-label post-market study, to evaluate the safety and efficacy of hyaluronic acid intralesional injection. This Expert panel agrees with the intention of manufacturer to evaluate further the medical device and recommends the development of a multicentre clinical registry including all treated patients with sufficient long-term follow-up.

2.4 Recommendations

The manufacturer should provide additional information about the potential pharmacological effects of HA.

Information about the degradation profile of the device as well as information of potential migration of the device should be provided.

The manufacturer should provide sufficient guidance for proper intralesional injection and clear warning to avoid the intravascular device injection.

In addition to the planned post market follow up study, the expert panel recommends the development of a multicentre clinical registry to ensure that sufficient long term follow up data is available.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable²
Has the Secretariat provided information from stakeholders?
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Summary of the information that was taken into account and how it was taken into account.
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
No divergent views

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.