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.

1 ADMINISTRATIVE INFORMATION

Date of reception of the dossier	05/11/2024
Notified Body number	2265
Internal CECP dossier #	EMA/EX/0000236104
Medical device type	Drug eluting stent
Intended purpose	Intended to improve coronary luminal diameter in patients with symptomatic ischemic heart disease.
Risk class / type	☒ class III implantable ☐ class IIb active device intended to administer or remove medicinal products(s)
Screening step: medical field / competence area	Circulatory system

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

2.1 Decision of the screening experts

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

Date of decision	20/11/2024
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)	
Not applicable	
Summary as to why there is intention to provide an opinion	
The device demonstrates a medium level of novelty in its composition and functionality. It incorporates the addition of two anticoagulants, rivaroxaban and argatroban, alongside the standard antiproliferative agent sirolimus, which introduces potential novel clinical and health impacts.	
Summary as to why there is *no* intention to provide an opinion	
Not applicable	
Any other comments	
Not applicable	

2.2 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 device has a medium to high degree of novelty due to its unique combination of antiproliferative and anticoagulant agents, which differentiates it from existing second-generation drug-eluting stents.
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
This device has the potential to minimize stent surface area thrombus locally in addition to the routine systemic anticoagulation provided during the stenting procedure, thus reducing the frequency of in-stent thrombosis. However, the integration of two anticoagulants in a stent coating raises significant questions about long-term efficacy and safety, including risks of increased bleeding or other anticoagulant-related complications.

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

2.3 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

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

3.1 Information on panel and sub-group

Date of opinion	10/01/2025
Expert panel name	Circulatory system
Sub-group of expert panel (where relevant)	Cardiovascular stents

3.2 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
This expert panel agrees with the notified body (NB)'s assessment that the clinical data presented by the manufacturer is adequate and sufficient to demonstrate safety and performance for DESyne BDS Plus. The CEAR provides sufficiently detailed information regarding the assessment of the NB and the conclusions drawn from the assessment. The main source of clinical data is the DESyne BDS Plus RCT, a prospective, multi-center, single-blinded, randomized clinical study. 200 patients (100 in each arm) were randomised in a 1:1 ratio (DESyne BDS Plus versus DESyne X2), requiring treatment of up to two de novo coronary artery lesions ≤ 34 mm in length in vessels ≥ 2.25 mm and ≤ 3.5 mm in diameter. The study was conducted in two parts, with the randomisation of the first 100 subjects (Cohort 1) followed by the randomization of an additional 100 subjects (Cohort 2). In addition, a PK sub-study enrolled 11 non-randomised subjects treated only with the DESyne BDS Plus device, with a maximum of 3 DESyne BDS Plus stents implanted. The primary endpoint of this study was subject-level target lesion failure (TLF) from the start of the procedure through 3 days or through hospital discharge, whichever came first. The secondary endpoint was late lumen loss (LLL) at six months. Additional clinical endpoints, including TLF and TVF at 12 months, were also included. From the conclusions in the CER and the CEAR, the DESyne BDS Plus demonstrated non-inferiority in both the primary and secondary endpoints as compared to DESyne X2. No additional risks associated with the addition of the two anticoagulants to the DESyne BDS Plus platform have been observed through the 12-month follow-up period.
2. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination
This expert panel agrees with NB's assessment of the manufacturer's benefit-risk determination of the device under conformity assessment.

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

For the clinical benefits, the following variables were considered: TLF (a composite of cardiac death, target vessel MI, or ischemia-driven TLR) or TVF (a composite of cardiac death, target vessel MI, or ischemia-driven TVR), TVR (target vessel revascularization) or TLR (target lesion revascularization), MACE (a composite of death, MI, or stroke), LLL (late lumen loss), binary restenosis, diameter stenosis, in-stent restenosis, definite or probable stent thrombosis and strut coverage.

For the clinical safety, the following outcome parameters were considered: clinical event rates through follow-up, unexpected adverse device effects, procedural complications (including but not limited to dissection, spasm, thrombus) and any other adverse events that may be related to the procedure or the device.

In the NB assessment, the overall residual risks were considered acceptable. No unexpected adverse events related to the use of DESyne BDS Plus device were observed through 12-month follow up in the DESyne BDS Plus RCT. The quantified risks (i.e., adverse events) of the DESyne BDS Plus device observed in the DESyne BDS Plus RCT were similar to or better than the comparator.

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 is to improve coronary lumen diameter, and the indications are symptomatic heart disease due to discrete de novo native coronary lesions, with a reference vessel diameter of $\geq$ 2.25 mm to $\leq$ 3.5 mm and lesion lengths $\leq$ 34mm. The stent is intended as a permanent implant. Limitations of use include stenosis of the left main coronary artery, stenosis involving bifurcations, >2 overlapping stents, in stent restenosis and graft stenosis.

The manufacturer sponsored only one clinical study using this device. Several other studies with similar stents (biodegradable and durable coatings and different active pharmaceutical agents like novolimus and sirolimus) from the same manufacturer have already been conducted, therefore, additional data could be used for the clinical assessment.

The clinical trial was a single-blinded, randomised, prospective, multicentre, 1:1 randomized trial, with 100 patients randomized to each group. The patient inclusion/exclusion criteria were aligned with the intended purpose of the device and the sought medical indications. The study evaluated various outcomes, including mortality, in-stent stenosis, and late lumen loss. Beyond the data generated by this specific study, the clinical evidence assessed included the results of a comprehensive literature review that was conducted to supplement the clinical evidence to support the intended purpose. This review provided a comparison of existing data on DES with the device under investigation. The expert panel considered the assessment of the literature review adequate.

This expert panel agrees with the assessment of the NB, that the clinical data presented for the assessment is consistent with the claimed intended purpose.

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

The expert panel considered that the assessment of the PMCF plan by the NB is sufficient but not very detailed. All the patients enrolled in the clinical trial will be followed up to 3 years. This was considered to be sufficient as all components of the device, except rivaroxaban and argatroban, were already assessed in several other clinical trials sponsored by the manufacturer or by other manufacturers of

devices used in similar clinical indications. All these devices have been on the market for several years and are already subject to regular PMS activities.

These data, along with information from adverse event reporting, and ongoing literature reviews, will be integrated into the CER and will be reported annually to the NB for review.

Rivaroxaban and argatroban have been studied in several trials using the oral formulations of these medicines, these medicines have not yet been used long term in stents and in this vulnerable patient population. For this reason, this panel would recommend a longer follow-up period of the DESyne BDS Plus cohort to collect long term safety data

In general, this panel agrees with the NB assessment of the proposed strategy presented in the PMCF plan.

3.3 Summary of expert panel opinion

This expert panel reviewed the CEAR issued by the NB, along with the Clinical Evaluation Report (CER) and the Clinical Evaluation Plan (CEP) submitted by the manufacturer.

The NB concluded that the data collected from the DESyne BDS Plus RCT is appropriate and adequate to support the intended purpose and the clinical indications.

The benefit-risk profile was considered acceptable as the results of outcome parameters were similar to or better than the results from comparable state-of-the-art devices.

The PMCF plan, although not very detailed, was considered adequate although a longer follow-up period is suggested by the panel.

In general, the panel agrees with the NB's clinical assessment of this device.

3.4 Recommendations

The expert panel opinion is in agreement with the assessment performed by the NB but recommends a longer follow up period of the patients enrolled in the DESyne BDS Plus RCT study than currently foreseen in the PMCF plan, in order to investigate long-term risks of using rivaroxaban and argatroban as ancillary medicines in this device.

3.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[2]
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.
N/A

[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.

3.6 Divergent positions in case no consensus was reached

Please indicate how many of the experts of the panel or sub-group had divergent views
None
Summary of divergent positions
N/A