ID	*Information Sheet*	*Revision Date*	*Rev. #*
IS4507	SSCP	05/09/2023	03

TITLE: TFE.1609.03 SSCP_ Protégé DEB PTCA

TITLE: Summary of Safety and Clinical Performance Protégé DEB PTCA dilatation catheters

TFE. 1609.03_Attachment to TFE.1602.10_CER Protégé DEB and Protégé NC DEB catheters

CONCERNING PROJECT / CHANGE / KEYWORD:

PREPARED BY
NAME: Richa Rohila **DATE: 08-08-2024**
FUNCTION: Depty. Manager Regulatory Affairs **SIGNATURE:**

COMMENTS / REMARKS: This document is an attachment to the CER. Signature approvals of the CER TFE.1602.10 signifies approval of this SSCP TFE.1609.03
……

APPROVAL / SUGGESTED DISTRIBUTION

NAME:	Alex Luijkx	**DATE:**
FUNCTION:	QA/RA manager	**SIGNATURE:**
NAME:	Dr Brijesh Mishra	**DATE:**
FUNCTION:	Clinical Research Manager	**SIGNATURE:**
NAME:	Dr Nancy Chugh	**DATE:**
FUNCTION:	Director Marketing - International Business and Clinical Initiatives	**SIGNATURE:**

SSCP

Summary of Safety and Clinical Performance

Protégé DEB PTCA dilatation catheters,

Protégé DEB and Protégé NC DEB

Basic UDI-DI: 872063420BMD-DEB6S

Table of contents

0 Purpose

The purpose of this document is to demonstrate that the Blue Medical Devices B.V. percutaneous transluminal coronary angioplasty (PTCA) drug eluting balloon (DEB) dilatation catheters, Protégé DEB and Protégé NC DEB, (Basic UDI-DI BMD-DEB; UDI-DI PROxxxx01 and PNCxxxx01, respectively), conform to Annex I of MDR 2017/745 concerning clinical safety and performance. In other words, that the benefit-risk ratio is acceptable under the normal conditions of the intended use. The evidence presented in this document is based on the clinical evaluation report, which is periodically updated with evidence obtained from the market. This includes post market clinical follow-up reports and the periodic safety updated report.

This Summary of Safety and Clinical Performance is intended for health care professionals.
The devices should only be used by physicians trained in the performance of percutaneous transluminal coronary angioplasty and is only obtainable upon prescription by a registered medical professional and/or medical institution. The devices are not intended to be used directly by patients and/or other lay persons and it does not concern a implantable device for which patients will be given implant cards. Therefore, no part is included in this Protégé (NC) DEB PTCA Catheters SSCP which would be applicable and/or intended for patients and/or lay persons, or which would be required to be made publicly assessable to patients and/or lay persons.

Summary of safety and clinical performance

Intended for health care professionals

1 Device identification and general information

1.1 Device trade name

The scope of this SSCP is/are the following medical device(s):
Device trade names : Protégé DEB and Protégé NC DEB

1.2 Manufacturer's name and address

The manufacturer of Protégé DEB and Protégé NC DEB PTCA catheters is:

Name	:	Blue Medical Devices B.V.
Person Responsible for Regulatory Compliance	:	Alex Luijkx
Contact person	:	Alex Luijkx
Visiting address	:	Panovenweg 7
Postal code	:	5708 HR
City	:	Helmond
Country	:	The Netherlands
Phone	:	+31(0)492 588 900
Website	:	www.translumina.com

1.3 Manufacturer's SRN

The manufacturer's Single Registration Number is:
SRN : NL-MF-000002976

1.4 Basic UDI DI

The Basic UDI DI of the Protégé DEB PTCA catheters is
Basic UDI DI : 872063420BMD-DEB6S

1.5 Medical Device Nomenclature description / text

The Protégé DEB medical devices nomenclature code used is:
Medical device Nomenclature code : UMDNS 17521
This code applies to Catheters, Angioplasty Balloon dilatation, Coronary Perfusing is for both Protégé DEB and Protégé NC DEB catheters (Protégé (NC) DEB).

Device group CND[1]: Cardiac angiography device
The CND/EMDN code of the device is C010401020101 describing: Angioplasty catheters, balloon dilatation, coronary/PTCA Balloon dilatation Catheter.

[1] The European Medical Device Coordination Group (MDCG) will use Italy's CND codes as the basis for the Eudamed device database nomenclature (at the time of this writing these were yet to be officially published).

1.6 Class of device

By application of the classification rules in Annex VIII of the Medical Device Regulations MDR 2017/745 Blue Medical Devices B.V. Protégé DEB and Protégé NC DEB are Class III medical devices according

- rule 6 (described as surgically invasive device for transient/impermanent use), as the device is intended for use in direct contact with the heart or central circulatory system.
- rule 14 (described as all other active devices) as the devices are a PTX (Paclitaxel) eluting PTCA catheter.

1.7 Year when the first certificate (CE) was issued covering the device

The first approval for CE under MDD 93/42/EEC for the Blue Medical Devices Protégé (NC) DEB devices, with 3 µg/mm^2 Paclitaxel dosage, was in July 2013.
The re-registration for CE under the MDR 2017/745 was obtained for the Blue Medical Devices Protégé (NC) DEB devices, with 3 µg/mm^2 Paclitaxel dosage, was in 2023 .

1.8 Notified body name and single identification number

Name Notified body : British Standards Institute (BSI)
Single identification number : 2797

2 Intended use of the device

2.1 Intended purpose

The Protégé and Protégé NC DEB PTCA catheters are intended for balloon dilatation of the stenotic portion of a coronary artery or bypass graft stenosis for the purpose of improving myocardial reperfusion in patients during a percutaneous coronary interventional (PCI) procedure in a blood vessel.
The Protégé and Protégé NC DEB PTCA catheters are intended for transient use (≤ 60 minutes).

2.2 Indication(s) and target population(s)

The Protégé DEB and Protégé NC DEB PTCA catheters are indicated for

- Balloon dilatation of the stenotic portion of a coronary artery or bypass graft stenosis, including in-stent restenosis (ISR), for the purpose of improving myocardial reperfusion in de novo lesions and small vessels (SVD).
- Pre- and post-balloon dilatation during coronary stent procedures.

The Protégé (NC) DEB PTCA catheter is intended to be used in patients suffering from stenotic lesions in the coronary vascular system who require a PCI.
The Protégé (NC) DEB PTCA catheter is introduced into, advanced through, and used in blood vessels.

2.3 Contraindications and/or limitations

The Protégé (NC) DEB PTCA catheters are contraindicated for:

- Intolerance or allergy to Paclitaxel
- The use of the Protégé (NC) and another drug releasing device like Drug Eluting stents or Drug Eluting Balloons within a period shorter than 90 days, including simultaneous use. Over-dosage or drug interaction cannot be excluded between multiple active agents.
- Unprotected left main coronary artery
- Coronary artery spasm in the absence of a significant stenosis
- Unprotected left main coronary artery
- Patients who are (potentially) pregnant

3 Device description

3.1 Description of the device

3.1.1 General device description

The Blue Medical Devices B.V. Protégé (NC) DEB PTCA catheters are rapid exchange (Rx) catheters with a semi-compliant (Protégé DEB) balloon or a non-compliant (NC) balloon (Protégé NC DEB) near the distal tip (**Figure 1**). The distal section of the outer lumen is used for inflation of the balloon, and the inner lumen permits the use of guidewires ≤0.014 inch (0.36 mm) to facilitate advancement of the catheter through blood vessels, to and through the stenosis or stent to be dilated. The proximal section of the catheter is a single-lumen, stainless steel Hypotube with a single luer port hub for inflation/deflation of the balloon. The balloon is designed to provide an inflatable segment of known diameter and length at recommended pressures. The DEB PTCA catheters are supplied with a balloon protector placed over the balloon to maintain a low profile and a eyed stylet is placed into the inner lumen to protect the patency of the catheter. The catheter tip is tapered to facilitate advancement of the catheter to and through a stenosis or stent. The shaft has a hydrophilic coating. The Protégé (NC) DEB PTCA catheters are afforded with an active component, Paclitaxel, which is incorporated in a coating on the balloon surface. On inflation of the balloon the coated surface comes in contact with the vessel and the incorporated Paclitaxel is delivered to the vessel wall. The total load of Paclitaxel is dependent on diameter and length of the Protégé (NC) balloon. The coated surface of the balloon holds 3µg Paclitaxel per mm². The Protégé (NC) PTCA catheter is for single patient, single procedure only.

All variants of Protégé DEB PTCA catheters with their Basic UDI-DI and UDI-DI identified in §1.4 are presented in **Table 1** (Protégé DEB [semi-compliant]) and **Table 2** (Protégé NC DEB [non-compliant]) below, with model (product family) name and UDI-DI number.

Device trade names : Protégé DEB and Protégé NC DEB

Table 1: *Protégé DEB (semi-compliant) sizes and Basic UDI-DI and UDI-DI*

Product family	Balloon diameter (mm)	Balloon length (mm)	Rev #	Basic UDI-DI	UDI-DI
PROTÉGÉ	2.0	10	01	872063420BMD-DEB6S	PRO201001
PROTÉGÉ	2.0	15	01	872063420BMD-DEB6S	PRO201501
PROTÉGÉ	2.0	20	01	872063420BMD-DEB6S	PRO202001
PROTÉGÉ	2.0	30	01	872063420BMD-DEB6S	PRO203001
PROTÉGÉ	2.5	10	01	872063420BMD-DEB6S	PRO251001
PROTÉGÉ	2.5	15	01	872063420BMD-DEB6S	PRO251501
PROTÉGÉ	2.5	20	01	872063420BMD-DEB6S	PRO252001
PROTÉGÉ	2.5	30	01	872063420BMD-DEB6S	PRO253001
PROTÉGÉ	3.0	10	01	872063420BMD-DEB6S	PRO301001
PROTÉGÉ	3.0	15	01	872063420BMD-DEB6S	PRO301501
PROTÉGÉ	3.0	20	01	872063420BMD-DEB6S	PRO302001
PROTÉGÉ	3.0	30	01	872063420BMD-DEB6S	PRO303001
PROTÉGÉ	3.5	10	01	872063420BMD-DEB6S	PRO351001
PROTÉGÉ	3.5	15	01	872063420BMD-DEB6S	PRO351501
PROTÉGÉ	3.5	20	01	872063420BMD-DEB6S	PRO352001
PROTÉGÉ	3.5	30	01	872063420BMD-DEB6S	PRO353001
PROTÉGÉ	4.0	10	01	872063420BMD-DEB6S	PRO401001

PROTÉGÉ	4.0	15	01	872063420BMD-DEB6S	PRO401501
PROTÉGÉ	4.0	20	01	872063420BMD-DEB6S	PRO402001
PROTÉGÉ	4.0	30	01	872063420BMD-DEB6S	PRO403001

Table 2: *Protégé NC DEB (non-compliant) sizes and Basic UDI DI and UDI DI*

Product family	Balloon diameter (mm)	Balloon length (mm)	Rev #	Basic UDI-DI	UDI-DI
PROTÉGÉ NC	2.5	10	01	872063420BMD-DEB6S	PNC251001
PROTÉGÉ NC	2.5	15	01	872063420BMD-DEB6S	PNC251501
PROTÉGÉ NC	2.5	20	01	872063420BMD-DEB6S	PNC252001
PROTÉGÉ NC	2.75	10	01	872063420BMD-DEB6S	PNC271001
PROTÉGÉ NC	2.75	15	01	872063420BMD-DEB6S	PNC271501
PROTÉGÉ NC	2.75	20	01	872063420BMD-DEB6S	PNC272001
PROTÉGÉ NC	3.0	10	01	872063420BMD-DEB6S	PNC301001
PROTÉGÉ NC	3.0	15	01	872063420BMD-DEB6S	PNC301501
PROTÉGÉ NC	3.0	20	01	872063420BMD-DEB6S	PNC302001
PROTÉGÉ NC	3.25	10	01	872063420BMD-DEB6S	PNC321001
PROTÉGÉ NC	3.25	15	01	872063420BMD-DEB6S	PNC321501
PROTÉGÉ NC	3.25	20	01	872063420BMD-DEB6S	PNC322001
PROTÉGÉ NC	3.5	10	01	872063420BMD-DEB6S	PNC351001
PROTÉGÉ NC	3.5	15	01	872063420BMD-DEB6S	PNC351501
PROTÉGÉ NC	3.5	20	01	872063420BMD-DEB6S	PNC352001
PROTÉGÉ NC	4.0	10	01	872063420BMD-DEB6S	PNC401001
PROTÉGÉ NC	4.0	15	01	872063420BMD-DEB6S	PNC401501
PROTÉGÉ NC	4.0	20	01	872063420BMD-DEB6S	PNC402001
PROTÉGÉ NC	4.5	10	01	872063420BMD-DEB6S	PNC451001
PROTÉGÉ NC	4.5	15	01	872063420BMD-DEB6S	PNC451501
PROTÉGÉ NC	4.5	20	01	872063420BMD-DEB6S	PNC452001

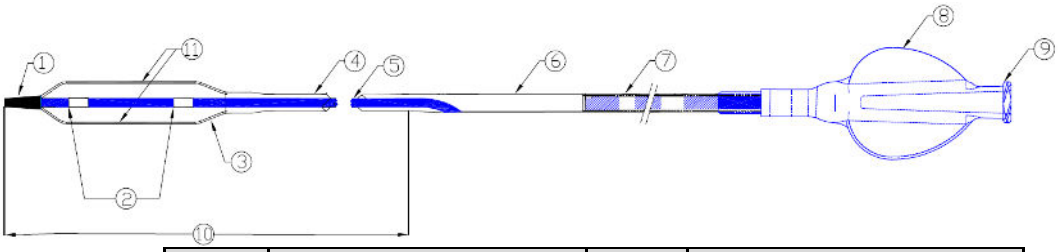
3.1.2 Principles of operation

The Protégé (NC) DEB PTCA dilatation catheter is advanced through the vasculature over a routinely used 0.014" guidewire. Under high quality fluoroscopic guidance, the catheter is advanced until the DEB PTCA balloon is positioned at the required location in the target lesion. The balloon is inflated (using standard coronary interventional technique by means of an inflation device) and the lesion dilated. The deflated balloon catheter is withdrawn.

3.1.3 Key functional elements

A schematic representation of the rapid exchange Protégé (NC) DEB PTCA catheter with indicated key functional elements is shown Figure 1.

Figure 1: *Schematic representation of the rapid exchange Protégé and Protégé NC DEB PTCA catheters*



No.	Figure Description	No.	Figure Description
1	Soft tip	6	Intermediate shaft
2	Radiopaque Marker Bands	7	Hypotube
3	Balloon	8	Luer Hub
4	Outer Body / Distal shaft	9	Luer Lock
5	Inner Body	10	Hydrophilic Coating shaft
		11	Paclitaxel on balloon surface

3.1.4 Materials in direct contact

Materials that come in direct contact with the patient (blood, heart vasculature, central circulating system) are:

- PTFE *Hypotube*
- Pebax *Outerbody, Intermediate Shaft, Soft-tip (tip tubing)*
- Pebax and HDPE *Innerbody*
- Polyamide composite material *Balloon material*
- Hydrophilic coating
- Paclitaxel on balloon surface

Materials that come in indirect contact with the patient are:

- PI/IR marker
- Polyamide luer lock

The contact duration of the materials is less than 60 minutes.
Sterilization of the devices: EtO for Protégé NC DEB and Gamma irradiation for Protégé DEB.

3.1.5 Special design attributes

3.1.5.1 Medicinal substances

Blue Medical Devices B.V. states that Protégé DEB and Protégé DEB NC PTCA catheters incorporate the medicinal substance Paclitaxel, an active component and is a known toxic substance, on the balloon surface. The purpose of Paclitaxel is to reduce the risk of target lesion restenosis (TLR), which means a lower risk for the patient of a reintervention/target lesion revascularization in the mid- and longer term .

3.1.5.2 Components of biological origin

Blue Medical Devices B.V. states that Protégé DEB and Protégé DEB NC PTCA catheters do not incorporate viable materials of animal origin.

3.1.5.3 Components of human origin

Blue Medical Devices B.V. states that Protégé DEB and Protégé DEB NC PTCA catheters do not incorporate tissues and/or blood derivatives of human origin.

3.1.5.4 Absorption/dispersion in the body

Blue Medical Devices B.V. states that Protégé DEB and Protégé DEB NC PTCA catheters contain substances that are absorbed or dispersed into the body during use.

3.1.5.5 CMR substances

Based on the biological safety evaluation and the characteristics of the body contacting materials, Blue Medical Devices B.V. states that Protégé DEB and Protégé DEB NC PTCA catheters contain a substance, Paclitaxel, that is potentially a genotoxic (in particular clastogenic) agent based upon its pharmacodynamic mechanism of action, which is interference with the microtubule disassembly. The relevance of this specific mechanism of genotoxicity for human carcinogenicity risk is currently not known.

3.2 Previous generation(s) or variants

The Protégé (NC) DEB catheters are Blue Medical Devices B.V. 1st generation DEB PTCA dilatation catheters and are based on the Blue Medical Devices B.V. non-drug coated 4th Generation PTCA balloon dilatation catheters, the difference being the addition of the Paclitaxel to balloon surface of the Protégé (NC) DEB catheters.

- The Protégé DEB semi-compliant is based on the Everest semi-compliant PTCA balloon dilatation catheter (basic UDI-DI: BMD-PTCA, UDI-DI: EVERxxxx01).
- The Protégé NC DEB non-compliant is based on the Force NC non-compliant PTCA balloon dilation catheter (basic UDI-DI: BMD-PTCA, UDI-DI: XFORxxxx01).

Except for the Paclitaxel on the 1st generation Protégé (NC) DEB catheters, the general device description (3.1.1) is applicable for all Blue Medical Devices B.V. PTCA balloon dilatation catheters.

Intended purpose, intended patient population, intended users and user environment are the same. The IFU only differ in the aspects related to the Paclitaxel.

Compared to the uncoated PTCA balloon catheters, the addition of Paclitaxel to the balloon (DEB) has the benefit of reducing the risk of restenosis following the balloon dilatation procedure in the longer term. The Paclitaxel uptake in the vessel tissue upon inflation inhibits smooth muscle cell migration and proliferation at the treated lesion location.

3.3 Accessories intended to be used in combination with the device.

Blue Medical Devices B.V. states that Protégé DEB and Protégé DEB NC PTCA catheters are intended to be used in accordance with established minimally invasive / coronary catheterization procedures, which includes the accompanying devices (guiding catheters, guidewires, balloon inflation device connection, hand syringes and contrast media) that are required to be used routinely in combination with the Protégé DEB and Protégé DEB NC PTCA catheters to be able to perform PCI procedures.

3.4 Other devices or products intended to be used in combination with the device

Not applicable, Blue Medical Devices B.V. states that Protégé DEB and Protégé DEB NC PTCA catheters are not intended to be used in combination with specific accessories other than generic devices routinely required for the interventional PCI/PTCA procedure as described in the directions of use.

4 Risks and warnings

4.1 Residual risks and undesirable effects

The Risk Management process has assured that the hazards (failure modes) which could lead to potential harms to the patient were identified, and all reasonably practicable activities (risks mitigation measures) have been implemented to achieve risk acceptability through safety by design and/or in-line process controls, and usability risk control measures to prevent the hazards from occurring.

Improper use and/or handling by the user/customer cannot be eliminated through safety by design and/or in-line process controls. Usability risk control measures (RCM), to prevent hazards from occurring, have been implemented by appropriate labelling and/or IFU (procedure) text.

The implemented control measures are outlined in the below table, which are covered in "warnings and precautions" as listed in section 4.2.

Potential harm	Implemented usability risk control measures in IFU and/or labelling	Occurrence rates (per unit sales) and source reference.	
		Official Complaints	Official Complaints + Pearl Study
Air-embolism	Instructions on preparation and that the use of the device is to be performed by qualified physicians.	0%	0%
Embolism	Instruction and/or warning and/or labelling on single use device, hub product identification, fluoroscopic control, catheter handling.	0%	0.01%
Major vessel dissection	Instructions and/or warnings on Rated Burst Pressure, compliance chart, fluoroscopic control, catheter handling.	0%	0%
Vessel perforation and/or rupture	Instructions and/or warnings on Rated Burst Pressure, compliance chart, fluoroscopic control, hub product identification, catheter handling.	0%	0%
Acute Myocardial Infarction	Instructions and/or warnings on Rated Burst Pressure, compliance chart, catheter handling.	0%	0%
Infection	Easy opening box, and Instructions and/labelling indicating single use, "use before date", rough handling, following hospital procedure.	0%	0%
Death	Instructions on procedure regarding in deflation, preparation device, catheter handling.	0%	0%
Occlusion of coronary artery/bypass graft	Instruction warning and labelling on single use device .	0%	0%
Additional percutaneous/surgical intervention	Instructions and/or labelling and/or warnings on device preparation, inflation & deflation procedure, hub product identification, Rated Burst Pressure, compliance chart, fluoroscopic control, catheter handling, "use before date".	0%	0%
Allergic or immunological reaction to drug or similar products	Instructions and/or warnings pertaining to drug or similar products.	0%	0%

Percutaneous devices used for dilatation of target lesions are an integral part of coronary catheterization. There are potential complications that could be encountered during all coronary catheterization procedures which cannot be further reduced by taking design and/or inline process controls risk mitigation measures and/or through protective measures or information for safety.
Therefore, potential complications (harms) that can be encountered during all coronary catheterization procedures (either with or without the application of angioplasty devices under normal conditions of use) are listed in the IFUs of the Blue Medical Devices Protégé DEB and Protégé DEB NC PTCA catheters.
These potential complications/ can include, but are not limited to:

- Death.
- Acute myocardial infarction.
- Total occlusion of the coronary artery or bypass graft.
- Coronary vessel dissection, perforation, rupture or injury.
- Restenosis of the dilated vessel.
- Haemorrhage or haematoma.

- Unstable angina.
- Arrhythmias, including ventricular fibrillation.
- Drug reactions, allergic reaction to contrast medium.
- Hypo/hypertension.
- Infection.
- Coronary artery spasm.
- Arteriovenous fistula.
- Embolism.

As a Paclitaxel drug-coating is applied to the balloon, pharmaceutical information is included in the IFU pertaining to the drug:
Minor traces of Paclitaxel in the blood plasma appear less relevant than for a systemic treatment. However, undesirable side-effects cannot be completely ruled out.

- Abnormal liver enzyme values.
- Allergic or immunological reaction to the drug or similar agents.
- Alopecia.
- Anaemia.
- Disorders of the heart conduction system.
- Gastro-intestinal tract impairment.
- Haematological dyscrasia (incl. leukotopenia, neutropenia, thrombocytopenia).
- Histological changes in the vascular wall, incl. inflammation, cell damage or necrosis.
- Myalgia / arthralgia.
- Peripheral neuropathy.
- Pseudomembranous colitis.

4.2 Warnings and precautions

Warnings and precautions related to the preparation of a device or relating to procedural steps are contained in the IFU.
The IFU can be assessed on the manufacturer's website: : www.translumina.com

Warnings

- For single patient, single procedure use only. Do NOT resterilize and/or reuse as this can potentially result in compromised device performance and increased risk of inappropriate resterilization and cross contamination.
- To reduce the potential vessel damage, the inflated diameter of the balloon should approximate the diameter of the vessel just proximal and distal to the stenosis.
- PTCA in patients who are acceptable candidates for coronary artery bypass graft surgery requires careful consideration. This includes possible hemodynamic support during PTCA as treatment of this patient population carries special risk.
- When the balloon dilatation catheter is exposed to the vascular system, it should be manipulated while under high quality fluoroscopic guidance. Do not advance or retract the catheter unless the balloon is fully deflated under vacuum. If resistance is met during manipulation, determine the cause of the resistance before proceeding.
- Balloon Pressure: do not exceed the rated burst pressure (RBP) indicated on the packaging. The rated burst pressure (RBP) is based on results of in vitro testing. At least 99.9% of the balloons (with a 95% confidence) will not burst at or below their rated burst pressure (RBP).

- Use of a pressure-monitoring device is recommended to prevent over pressurization.
- PTCA should only be performed at hospitals where emergency coronary bypass surgery can be quickly performed in the event of a potentially injurious or life-threatening complication.
- Use only the recommended balloon inflation medium. Never use air or any gaseous medium to inflate the balloon.
- Use the catheter prior to "Use Before" ("expiry") date specified on the package.
- Treatment of vessels with moderate or heavy lesion calcification is associated with decreased success rates up to 60-85% and increases the risk of acute closure vessel, trauma, balloon burst, balloon entrapment and associated complications.
- Paclitaxel is in potential a genotoxic (in particular clastogenic) agent based upon its pharmacodynamic mechanism of action, which is interference with the microtubule disassembly. The relevance of this specific mechanism of genotoxicity for human carcinogenicity risk is currently not known.
- Breastfeeding should be withheld for at least 6 days after treatment.

Interactions with other drugs

The total load of Paclitaxel is only a fraction of less than 0.02% of the volume generally applied in chemotherapies. The risk of interactions with other active agents is therefore high improbable. Nonetheless caution should be exercised when concurrently administering known CYP3A4 and/or CYP2C8 substrates (like cyclosporine, lovastatin, midazolam, ondansetron, terfenadine) or drugs with high PPB (like sulfonureas, coumarin type anti-coagulants, digitoxin, salicylic acid, sulfonamides) the specific instructions for use for these active agents should be consulted in addition.

Precautions

- Prior to angioplasty procedure, the catheter should be examined to verify functionality and ensure that its size and shape are suitable for the specific procedure for which it will be used.
- Only physicians trained in the performance of percutaneous transluminal coronary angioplasty should use the catheter.
- Direct touching of the balloon, wiping of balloon surface or contact with organic solvents, e.g. alcohol, should be strictly avoided, since this can cause delamination of the balloon coating.
- During the procedure, appropriate anticoagulant and coronary vasodilator therapy must be provided to the patient as needed. Anticoagulant therapy should be continued for a period of time to be determined by the physician after the procedure.

4.3 Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN)

Not applicable. There were no FSCA.

5 Summary of clinical evaluation and post-market clinical follow-up (PMCF)

The conformity to the GSPR of the Protégé DEB and Protégé NC DEB PTCA dilatation catheters was assessed and endorsed by the Notified Body based on the clinical data forming the clinical evidence, the evaluation of undesirable side-effects and the acceptability of the benefit-risk ratio.

5.1 Summary of clinical data related to the equivalent device

Not applicable.

5.2 Summary of clinical data from conducted investigations of the device before the CE-marking

No clinical investigations were conducted with the Protégé (NC) DEB PTCA catheters, with drug load 3 µg/mm^2, prior to CE-certification (MDD 93/92/EEC) in 2013.

5.3 Summary of clinical data from other sources

5.3.1 Systematic literature review

In the published literature there were one references specifically to the Blue Medical Devices Protégé (NC) DEB PTCA catheters.

Reference Pleva et al. (2017) BMC Cardiovasc. Disord. 17(1);1–9: A registry of 12-month data performed by Pleva et al. compared different PEBs in the treatment of Bare Metal Stent (BMS) in-stent restenosis (ISR). Pleva et al prospectively collected data for Blue Medical Devices Protégé DEB (wing-seal) (PEB) (n=64) and compared this with control data from another study involving SeQuent Please DEB (iopromide-DEB) (n=68) and an Everolimus eluting stent (EES) (n=68). At 12-months MACE rate was significantly lower in the iopromide-DEB group (10.2%) compared to Protégé DEB (PEB) (26.6%) and EES (19.2%). The MACE rate reported by Pleva et al. for the Protégé DEB is not in line with the recent PEARL real-world registry outcomes at 2-years follow-up of 513 patients treated for lesions in ISR (n=382) (unpublished data PEARL registry, 2021, see section below). In the Pearl registry complex group of patients, the incidence of MACE at 2-years was 17.1% in patients treated for in-stent restenosis. Incidence of ISR TLR was 11.7%. (Pleva et al. report on TVR.) History of coronary artery bypass grafting and lesion length were predictors of MACE in patients treated for in-stent restenosis. *In conclusion*, given the presented Pearl study clinical data and comparison to the literature reported data on treatment of any (all) ISR with DEB, as well as separate data on BMS-ISR and DES-ISR, the Pearl study Protégé DEB data supports the acceptability for the safety and performance of the Protégé DEB according the relevant GSPR. The Protégé DEB data performance objective (acceptance criteria mean ≤15.6%) for all ISR TLR (BMS-ISR + DES-ISR) at ≥12-24 months was achieved with a TLR of 11.7%, as presented with the PEARL registry clinical data.

5.3.2 Investigator-initiated study

In 2014, an investigator-initiated, multicenter, prospective one-arm observational clinical registry (the Netherlands) to compare safety and efficacy of a Paclitaxel-eluting angioplasty balloon to the current literature in the real-world (PEARL registry) commenced. Dr. A. IJsselmuiden (Amphia Hospital Breda, the Netherlands) is Principal Investigator. Four Dutch hospitals participated in this trial. The last patient was included in 2019 (n=513).

The study DEB devices were the Protégé DEB and Protégé NC DEB PTCA catheters.

All patients signed informed consent. The PEARL trial was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of each participating centre.

Reference Vlieger et al. (2022): Vlieger, Selina & Cheng, Jin & Oemrawsingh, Rohit & Weevers, Auke & Polad, Jawed & Gho, Ben & Meuwissen, Martijn & Heijer, Peter & Boersma, Eric & Ijsselmuiden, Alexander. (2022). Clinical Performance of a Paclitaxel Drug-Coated Balloon in Real-World Percutaneous Coronary Intervention Practice: The PEARL Registry. The Journal of invasive cardiology. 34. E462-E468. 10.25270/jic/21.00339.

Randomized controlled trials for in-stent restenosis (ISR) and de novo lesions in small-diameter vessels have shown promising results, but data on DCB use in real-world practice are still scarce. The aim of the PEARL (Paclitaxel-Eluting Angioplasty Balloon in the Real-World) registry was to evaluate the safety and efficacy of a paclitaxel DCB in real-world percutaneous coronary intervention (PCI) practice. Between 2014 and 2019, a total of 513 patients treated with the

Protégé paclitaxel DCB (Wellinq) were prospectively included at 4 hospitals in the Netherlands. The primary endpoint was 2-year major adverse cardiac event (MACE), defined as cardiac death, target-vessel myocardial infarction, or target-lesion revascularization (TLR). DCB was used for ISR in 382 patients and for de novo lesions in 131 patients. Acute coronary syndrome was the reason for presentation in 58.9% of patients. At lesion level, 34.1% of lesions were classified as type B2 and 36.1% as type C. Predilation was performed in 62.2% and noncompliant DCB was used in 40.7% of lesions. DCB-related procedural complications were infrequent (3.3%, mostly coronary dissection [2.3%]). Bailout stenting was required in 3.1%. MACE during 2-year follow-up occurred in 17.1% of patients treated for ISR and 9.7% of patients treated for de novo lesions. The incidence of TLR was 11.7% of ISR patients and 2.9% of de novo patients. History of coronary artery bypass grafting and lesion length were predictors of MACE in patients treated for ISR. The use of Protégé paclitaxel DCB for PCI of ISR and de novo lesions is safe and effective during 2-year follow-up

Blue Medical contributed to the study by means of a research grant to set-up the PEARL registry. The principle investigator and co-investigators, declare to have no conflicts of interest as stated in publications related to the PEARL study.

5.3.3 PMCF procedure data

Aim: In 2017, a prospective single-centre in Austria, Protégé DEB (semi-compliant) PTCA catheters were evaluated for procedure performance and safety according to routine clinical practice.
Procedure: In 21 patients, 29 lesions were treated with 29 Protégé DEB catheters. In 4 patients, 2 balloons were used; and in one patient, one balloon for 2 target vessels. Of the 29 lesions treated, 51.7% were in the LAD; the lesions were type B1 (40.7%), B2 (14.8%) and C (14.8%). Vessel tortuosity was sever in 37.9% and moderate in 51.7%. Vessel angulation, 45-90° in 44.8%, and >90° in 24%. The majority (82.3%) of lesions showed the presence of calcification. Thrombus was present in 6.9%. PCI for ISR or de novo lesion was not recorded. Average maximum inflation pressure was 18 bar (the majority above the IFU specified RBP of 16 bar), with average 1.1 inflations/balloon.
Performance: Positioning of the balloon in the target lesion was judged as easy in 58.6%, and moderate in 37.9%. All catheter characteristics (positioning, flexibility, profile, crossability, trackability, deflation, balloon rewrap) were evaluated as good. Balloon integrity was maintained even though the inflation RBP was exceeded (warning in IFU not to exceed RBP).
Safety: There were no device -related events or complications reported.
Conclusion: The data indicates that the Protégé DEB PTCA catheter shows good clinical performance, without safety issues, for the intended patient population. There were no (adverse) events/complications reported and no new risks were identified.

5.3.4 PMS feedback from distributors in various countries in- and outside of Europe

Title	Description
Customer Feedback Survey Blue Medical Products (Protégé & Protégé NC) (2018)	Multi-distributor active feedback; Protégé n=9, Protégé NC, n=10. For the Protégé (semi-compliant), analysis of the data indicates overall performance as excellent and good, in total 67% of responses, and average in 33%. Analysis of the data indicates overall performance of the Protégé NC was excellent and good, in total 70% of responses, and average in 20%.
Customer Feedback Survey Blue Medical Products (Protégé & Protégé NC) (2019)	Multi-distributor (n=10) active feedback; Feedback n-6 on Protégé, n=10 on Protégé NC. Protégé DEB: Analysis of data indicates overall performance and Trackability over the wire scored excellent-to-good by all distributors. Other performance characteristics all scored excellent-good in >67%. There were no poor ratings. Protégé NC: Analysis of data indicates overall performance and all other performance characteristics scored excellent to good (≥80%). Parameters which scored a poor rating were crossability (lesion/stent), balloon profile, and balloon rewrap, with no further comments given. These ratings are the same or slightly better compared to 2018.
Annual PMS reports DEB 2017, 2018 and 2019	To assess whether a product continuously meets the User Requirements i.e. is still considered a State of the Art product. To assess the Quality, Safety & Performance, & Usability. PMS Data was reviewed and no issues were identified that might lead to safety or performance hazards. Data was compared to the information from the Risk Management file. No issues were identified that might lead to safety or performance hazards. There is no change in Benefit-Risk of the DEB catheters.
Customer Feedback Survey Blue Medical Products (Protégé & Protégé NC) (2023)	Multi-distributor (n=7) active feedback; Feedback n-3 on Protégé, n=4 on Protégé NC. Overall performance was judged as "good" for all devices. 3 Protégé NC and 2 Protégé DEB (SC) were used for post-stent dilatation. The post-dilatation by the Protégé NC was judged as excellent. Almost all characteristics were mainly judged as good, except for balloon rewrap, which was judged as acceptable (=average) for all balloons. No additional comments were given. There were no safety issues reported.
Annual PMS reports DEB 2023	To assess whether a product continuously meets the User Requirements i.e. is still considered a State of the Art product. To assess the Quality, Safety & Performance, & Usability. PMS Data was reviewed and no issues were identified that might lead to safety or performance hazards. Data was compared to the information from the Risk Management file. No issues were identified that might lead to safety or performance hazards. There is no change in Benefit-Risk of the DEB catheters.

5.3.5 Blue Medical Devices B.V. Complaints reported data for Protégé DEB and Protégé NC DEB PTCA catheters:

In total n=7 complaints were received by Blue Medical Devices complaints department since the device has been on the market (2013-2023) involving the catheter and/or packaging:

- n=5 complaints involved the catheter itself (listed in the below table);
- n=2 complaints concerned pre-procedure visual product anomalies.

The investigator-initiated registry, PEARL, indicated n=2 balloon burst (no patient harm), however these were not reported to Blue Medical Devices.

Based on the total units sold, the overall occurrence rate is 0.036. None (0%) of the complaints were reported to have resulted in patient harm.

Identified Device-related *procedure* failures (Hazards)		
Failures for PTCA balloon devices reported in FDA Maude database	**Protégé DEB (SC and NC) [overall: n/total sales=%] Reported failures since marketed (2013)**	
Balloon Rupture	Balloon burst. (n=3) [0.01%] (no patient injury reported)	Source: n=2 Pearl registry data, n=1 customer complaint

Material Split/cut or Torn/Puncture/Hole	-	
Material Rupture (Shaft/balloon)	-	
Detachment of Device or device Component	Break -> due to kink; detachment component (distal section *inside* guide catheter)) (n=1) [0.005%] (no patient injury reported)	Source: Complaint to Blue Medical Devices
Deflation Problem	-	
Difficult to Remove	-	
Entrapment of Device	-	
Difficult to Advance	-	
Failure to Advance	Crossability problems (n=3); (n=1). [0.02%] (no patient injury reported)	Source: n=2: Complaint to Blue Medical Devices n=1: Pearl study
Material Integrity Problem	-	
Material Deformation	-	
Failure to Fold	-	
Inflation Problem	-	
Device Damaged by Another Device	-	
Fracture Shaft	Break hypotube (due to kink) in section *outside* Guide Catheter (n=1) [0.005%] (no patient injury reported)	Source: Complaint to Blue Medical Devices
Improper or Incorrect procedure (not following IFU/labelling)	-	
Pre-procedure fracture (catheter damage)	-	

There were no Field Safety Corrective Actions (FSCA) during the life-time of the device as a result of complaints with clinical risks. All identified hazards and possible complications (risks) have been taken into account in the Risk Management Process of the Protégé DEB and Protégé NC DEB PTCA catheters.

Summary conclusion: The clinical data generated for the Protégé DEB and Protégé NC DEB PTCA catheters covers all safety aspects for the clinical application of the devices and gives confirmation on the clinical safety of the devices for the intended purpose (use).

The conformity to the GSPR of the Protégé DEB and Protégé NC DEB PTCA catheters was assessed and endorsed by the Notified Body based on the clinical data forming the clinical evidence, the evaluation of undesirable side-effects and the acceptability of the benefit-risk ratio.

5.4 An overall summary of the clinical performance and safety

The clinical safety and performance data generated for the marketed Protégé DEB and Protégé NC DEB PTCA catheters covers all performance aspects for the clinical application of the devices and gives confirmation on the safety and performance of the devices for the intended purpose (use). The safety and performance results in the Protégé DEB and Protégé NC DEB PTCA catheters clinical data sets presented, as well as other PMS feedback, shows acceptability of all performance characteristics and safety.

The claimed clinical benefit is supported by the documented clinical data:

- Balloon dilatation of the target lesion with concomitant release to the vessel wall of the antiproliferative drug, paclitaxel, with the benefit of a lower risk of target lesion restenosis (TLR) post-procedure in the mid- and longer term (>6 months) when compared to the TLR

outcomes of non-drug coated balloon dilatation (conventional PTCA/POBA) (<40% TLR) as reported in the literature. This means for the patient a lower risk of a reintervention due to TLR.
Data analysis outcome: Protégé (NC) DEB device TLR of <7% at 6-months and 14.9% at 2 years (cumulative denovo/ISR).

The claimed clinical performance objectives are supported by the Protégé (NC) DEB clinical data:

- *Procedure Objectives:* Following successful guidewire crossing of the lesion, technically successful DEB PTCA catheter procedure (delivery, lesion crossing, inflation/deflation, rewrap, removal).
  Data analysis procedure outcome: Achieved procedure Protégé (NC) DEB device success (technical) is 99.4% (*acceptance criteria based on SoA: 95%*)
- *Performance objectives Mid-longer term follow-up:*
  - Lower rate of repeat target lesion restenosis (TLR) during follow-up (>6 months following the angioplasty procedure with Protégé (NC) DEB PTCA catheter) compared to non-coated PTCA angioplasty (conventional balloon angioplasty / POBA);
    Data analysis outcome: Protégé (NC) DEB device TLR of <7% at 6-months and 14.9% at 2 years (cumulative denovo/ISR) (*acceptance criteria based on POBA devices SoA:<40%*)
  - TLR outcomes (≥6 months and 12-24 months follow-up) comparable to DEB PTCA catheters as reported in the literature.
    Data analysis performance mid-longer term outcomes:
    - At 6-months Protégé (NC) DEB showed an overall (all lesion types) TLR of 5% (*acceptance criteria ≤10% based on SoA literature*);
    - At 2 years follow-up (ISR), the Protégé (NC) DEB overall BMS-ISR/DES-ISR TLR was 11.7% *(acceptance criteria based on SoA literature: All (any) ISR, mean ≤15.6%)* (81% of stents were DES)
    - At 2 years follow-up (de novo lesions), the Protégé (NC) DEB incidence of de novo lesions TLR was 2.9% (*acceptance criteria based on SoA literature: mean ≤7.3%*).

The claimed clinical safety objective is supported by the documented data:

- Uneventful (safe) removal of the balloon catheter from the patient following a procedure with the DEB PTCA balloon catheter.
  Data analysis safety outcome: Protégé (NC) DEB PTCA catheter clinical data showed that there were no device-related serious adverse events during the balloon angioplasty procedure (0%) (*acceptance criteria based on SoA literature: Completion of procedure without device-related procedure serious adverse events (<1%)).*

5.5 Overall conclusion of the Benefit/Risk acceptability assessment:

Based on the data available in the current literature, and the assessment of the accumulated Blue Medical Devices Protégé (NC) DEB PTCA catheters clinical data, the *procedure risks* associated with the Blue Medical Devices Protégé (NC) DEB PTCA catheters are anticipated to be no greater than those associated with other intravascular devices (conventional PTCA balloon catheters and drug coated PTCA balloon catheters) intended for the balloon dilatation in the coronary artery for the purpose of improving myocardial reperfusion during a PCI procedure.
Based on the data available in the current literature, and the assessment of the accumulated Blue Medical Devices Protégé (NC) DEB PTCA catheters clinical data, the *mid- and longer term risks* associated with the Blue Medical Devices Protégé (NC) DEB PTCA catheters following a balloon angioplasty procedure are anticipated to be lower than a conventional PTCA balloon catheter and comparable to those associated with comparable SoA DEB intravascular devices.

The Blue Medical Devices Protégé (NC) DEB PTCA catheters, feature design characteristics that are beneficial in terms of deliverability, lesion crossability, lesion dilatation, balloon rewrap, retraction, a-traumatic catheter tip and body, ease of handling and use, and reduced risk of target lesion restenosis in the mid- and longer term.
Conclusion of the Benefit/Risk assessment: the overall residual risk is acceptable when weighed against the benefit.

5.6 Summary of evaluation of undesirable side-effects

The hazards (failure modes) which could lead to potential harms to the patient were identified, as given in the table in section 4.1 and all reasonable practicable activities (risks mitigation measures) were implemented to achieve risk acceptability by safety by design and/or in-line process controls and usability risk control measures to prevent the hazards from occurring. Of the potential harms, the only reported occurrence was embolism during angioplasty (Pearl study), without serious patient injury. This occurrence (0.01%) was evaluated and remained within the acceptance criteria.
The risk of mid-and longer term target lesion restenosis (TLR) is present following any balloon angioplasty procedure, irrespective of the absence or presence of an antiproliferative drug on the surface of the balloon. This risk of TLR is therefore also present for the Protégé (NC) DEB catheters, however, with the presence of the drug Paclitaxel on the balloon the risk of (repeat) revascularization for the patient is reduced when compared to a conventional non-coated PTCA balloon. The Protégé (NC) DEB catheter shows a lower risk of TLR than conventional PTCA balloon angioplasty, and a comparable risk to other marketed DEB catheters.
The low concentration of Paclitaxel (3µg/mm^2) present on the balloon surface is released into the vessel wall upon dilatation of the balloon. Allergic reaction is a known, and is given as a contraindication to Protégé (NC) DEB application in the IFU. To the best of our knowledge, there are no reports of systematic adverse events of the Paclitaxel released during coronary angioplasty in the mid- and longer term.
All percutaneous devices used in coronary catheterization procedures are for single use / single procedure only and must not be resterilized and/or reused as this could potentially result in compromised device performance and increased risk of inappropriate resterilization and cross contamination. A warning is included in the labeling/IFU.
The individual and overall residual risks are determined not to be different compared to the state of the art.

5.7 Ongoing or planned post-market clinical follow-up

As part of the Post Market Surveillance program, Blue Medical Devices B.V. will continue performing annual Post Market Clinical Follow-Up (PMCF) in the form of a user-survey(s) on Protégé DEB and Protégé NC DEB PTCA catheters to obtain continuous extensive customer feedback on procedure safety and performance, and usability. The analysis of the Protégé DEB and Protégé NC DEB PTCA catheters clinical data collected to date (including recent 2 year follow-up data of 513 patients) does not indicate the need for a PMCF study with short- or long-term post-procedure follow-up with the Protégé DEB and Protégé NC DEB PTCA catheters at the present. The PMCF study with post-procedure follow-up is continually assessed on the basis of customer survey and feedbacks according to the risk management process.
Based on the outcome of the risk management process, there are no residual risks or uncertainties or unanswered questions that would require specific evaluation during PMS.

6 Possible diagnostic or therapeutic alternatives

State of the Art literature indicates a number of alternative treatments and/or devices:

- Coronary drug-eluting stents (DES) are the most widely used intracoronary devices in PCI due to improved *longer term* clinical outcomes.

- Coronary Artery Bypass Grafting (CABG) has been considered the standard of care for patients with unprotected left main (LM) CAD (i.e. patients without prior CABG or a patent graft to the left anterior descending (LAD) or left circumflex artery), a reasonable alternative to CABG is PCI to improve survival in selected stable patients who have ≥50% diameter stenosis and either of the following:
    - Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (e.g. stenosis of the ostium or trunk vs distal bifurcation or trifurcation stenoses)
    - Clinical characteristics that predict a significantly higher risk of adverse surgical outcomes

  A consideration in the choice of CABG rather than PCI is if the patient does not tolerate or comply with dual antiplatelet therapy (DAPT).
- Rotational and Orbital Atherectomy. Atherectomy can be used for specific lesions unsuitable for balloon angioplasty and stent.
- Cutting and scoring PTCA catheters are balloon lesion-tipped catheters with respectively cutting (micro-blades) and scoring elements attached, which are used in those circumstances where a lesion is resistant to high pressure balloon dilatation.
- Medical therapy is recommended as first-line therapy in patients with stable angina unless one or more of the following indications for cardiac catheterization and PCI or CABG are present:
    - Severe symptoms
    - A change in symptom severity
    - Failed medical therapy
    - High-risk coronary anatomy or noninvasive findings
    - Worsening left ventricular dysfunction

Reference: Medical Society Guideline: F.-J. Neumann *et al.*, "2018 ESC/EACTS Guidelines on myocardial revascularization The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the," *Eur. Heart J.*, vol. 40, no. 2, pp. 87–165, 2019, doi: 10.1093/eurheartj/ehy394.

7 Suggested profile and training for users

The target users are medical professionals who perform and assist in catheterization procedures in a clinical laboratory setting, during percutaneous intervention (e.g. PTCA, coronary stent placement). Use of the product is restricted to healthcare professionals in an interventional suite with angiography equipment, with personnel with relevant and adequate training and who familiar with the possible/conceivable complications. The Blue Medical Devices DEB PTCA catheter can only be purchased on prescription of a physician.

8 Reference to any harmonized standards and CS applied

Key applicable (harmonised) standards and guidance documents specifically for PTCA:

- ISO 10555-1:2023 Intravascular catheters – Sterile and single-use catheters – Part 1: General requirements
- ISO 10555-4:2023 Intravascular catheters – Sterile and single-use catheters – Part 4: Balloon Dilatation Catheters
- ISO 10993-1:2018 - Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process

- ISO 10993-4:2017 - Biological evaluation of medical devices Part 4: Selection of tests for interactions with blood
- ISO 10993-5:2009 - Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity.
- ISO 10993-7:2008/A1:2019 - Biological evaluation of medical devices Part 7: Ethylene oxide sterilization residuals
- ISO 11135:2014/A1:2018 - Sterilization of health-care products - Ethylene oxide - Requirements for the development validation and routine control of a sterilization process for medical devices
- ISO 11607-1:2019/A1:2023 - Packaging for terminally sterilized medical devices. Part-1 Requirements for materials, sterile barrier systems and packages systems
- ISO 11607-2:2019/A1:2023 - Packaging for terminally sterilized medical devices. Part-2: Validation requirements for forming, sealing and assembly processes
- ISO 80369-7:2021 Small-bore connectors for liquids and gases in healthcare applications — Part 7: Connectors for intravascular or hypodermic applications

9 Revision history

SSCP Revision number	Date issued	Change description	Revision validated by the notified body	
01	XX-08-2021	First issue	X	Yes Validation language: English
			☐	No (only applicable for class IIa or some IIb implantable devices (MDR, Article 52 (4) 2nd paragraph) for which the SSCP is not yet validated by the NB)
02	XX-XX-XXXX		☐	Yes Validation language: English
			☐	No (only applicable for class IIa or some IIb implantable devices (MDR, Article 52 (4) 2nd paragraph) for which the SSCP is not yet validated by the NB)
03	08-08-2024	Review and update for the fiscal year 2023.	☐	Yes Validation language: English
			☐	No (only applicable for class IIa or some IIb implantable devices (MDR, Article 52 (4) 2nd paragraph) for which the SSCP is not yet validated by the NB)