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Life Restoring Technologies

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JOTEC GmbH | Lotzenäcker 23 | 72379 Hechingen | Germany
[redacted]

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Hechingen, 2020-09-23

Urgent Field Safety Notice

concerning

E-ventus BX Peripheral Stent Graft System

Dear valued customer,

With this letter we would like to inform you that JOTEC GmbH has decided to issue a Field Safety Corrective Action (FSCA) by means of a Field Safety Notice (FSN) to emphasize the risks of off-label use within the distributed countries. The description and justification of the planned action can be found in the following section.

Address

Clinical users, responsible person in the area of purchasing and logistics, dealers/distributors

Details on affected devices

E-ventus BX Peripheral Stent Graft System

[redacted]

Nr.	DEP
Ingenomen 28 SEP 2020	PARAAF
Relatie	d.d.
Melding	

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Background information and reason for the FSCA

- **Device description**

The E-ventus BX Peripheral Stent Graft System is manufactured by Bentley InnoMed GmbH under an OEM agreement for JOTEC GmbH.

The risk management for the E-ventus BX Peripheral Stent Graft System is performed in cooperation with Bentley InnoMed GmbH to cover the entire scope of the product. All product-related complaints and incidents reported to JOTEC GmbH are considered in the ongoing risk assessment of the E-ventus BX Peripheral Stent Graft System.

The intended purpose is defined as follows in the Instructions for Use (BX/04.2018-4 Art. No.: 904806):

The E-ventus BX Peripheral Stent Graft System is indicated for intraluminal chronic placement in iliac and renal arteries for:

- Restoring and improving the patency and
- Treating aneurysms, acute perforations, acute fractures and fistulas.

The following table summarizes the quantity of E-ventus BX Peripheral Stent Graft Systems placed on the market by JOTEC GmbH.

Table 1: Quantity of sold units E-ventus BX Peripheral Stent Graft System

Region	2015	2016	2017	2018	2019	2020-YTD*	Total
Germany	1417	1776	1767	1849	1758	903	-
EEA (without Germany)	1558	2011	2258	2594	1939	993	-
ROW (without Germany+ EEA)	158	259	519	416	686	371	-
Total	3133	4046	4544	4859	4383	2267	25175

*as of July 31, 2020

Background information on reported incidents and implemented actions

- **Risk Analysis & CAPA**

JOTEC GmbH has become aware by means of reported incidents of the fact that in a very small number of cases stent fractures and endoleaks IIId may occur due to off-label use of the medical device.

In the device risk management JOTEC GmbH has identified that one of the potential hazards of off-label use may be a failure of the stent graft when used in combination with other products outside the defined indication.

There are several potential hazardous situations to off-label use:

- Stent fracture (individual struts or fracture into multiple pieces)
- Damage to the sheathing / Endoleak type IIId

These hazardous situations can cause the following potential harms:

- Reintervention
- Aneurysm growth
- Aneurysm rupture
- Death

Following initial reports of complications in off-label use, a CAPA investigation in May 2015 by Bentley InnoMed GmbH did not identify any systematic device failure, nor could it be assumed that there was any malfunction, incorrect labeling or incorrect instructions for use. The off-label cases were included in the risk analysis.

Furthermore, a very stringent, continuous post-market surveillance and evaluation of all new off-label complaints has been established as a measure to compare the performance and safety of the medical device on a regular basis with the risk analysis and the risk/benefit ratio and to re-evaluate them as appropriate. This systematic approach enables appropriate measures to be taken at any time and in a timely manner in the event of an emerging trend.

In October 2015, an existing project for the E-ventus BX Peripheral Stent Graft System was implemented: Based on the harmonized standard "ISO 14971:2012 - Medical devices - Application of risk management to medical devices" and in connection with the foreseeable misuse (off-label), design optimization was carried out to reduce the probability of adverse events for this misuse (off-label).

The following changes were made:

1. Adjustment of the design of the distal stent end to the proximal stent end (ePTFE tubing can now be wrapped around both stent ends, i.e. identical fixation of the ePTFE tubing at the distal and proximal stent ends) to prevent stripping of the graft material e.g. during insertion through the Introducer Sheath.
2. Using ePTFE tubing twice as thick as before to improve the mechanical stability of the stent graft in aneurysms (also in off-label applications when used as a "bridging" stent graft).
3. Widening the connector bars on the stent by 20µm to increase the longitudinal stiffness of the stent graft (on repeated passing with a balloon catheter).

Additionally, in coordination with the "Regierungspräsidium Tübingen", the instructions for use have been updated to clearly point out the risks associated with off-label use/misuse in Chapter 4, Warnings and Precautions:

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4. Warnings and Precautions

The medical techniques and procedures described below do not entail all the PTA procedures acknowledged in medicine.

- Any use of the E-ventus BX Peripheral Stent Graft System for procedures other than those indicated in these instructions are not recommended.
- It is explicitly advised that the product is not designed and tested to be used beyond the approved indications (e.g. in the central circulatory system). The manufacturer shall not be liable if the product is used beyond the approved indications. In this case, the treatment is at the sole responsibility of the treating physician.

Figure 1: Excerpt from the instructions for use, Version BX/04.2018-4

- **Clinical Evidence**

The Clinical Evaluation Report, which was last updated in 2019 and complies with MEDDEV 2.7/1 rev., addresses the issue of off-label use and the potential risks associated with it. A literature review on the frequency of stent fractures in bridging stent graft EVAR applications was conducted. The case numbers from the literature are difficult to evaluate due to their complexity, but it was found that stent fractures occur when using peripheral stent grafts in EVAR applications. Publications with the highest case numbers suggest that the frequency is within the range of 0-2.3%.

The clinical evaluation found that a common off-label use for stent graft systems is seen in fenestrated or branched endovascular aortic repair (fEVAR/bEVAR) procedures. In such procedures, balloon-expandable stent grafts are used as bridging stent grafts in order to connect the target vessel with the main body of the aortic graft device. Those constructs exclude the aneurysm while preserving the organ perfusion. Currently, there are no dedicated bridging stent grafts available on the market which explains the off-label use of several types of self-expanding and balloon-expandable stent graft systems and established this practice. Literature indicates that perioperative mortality ranges between 4-7% and is therewith comparable to open surgery. Cases of endoleaks leading to the death of patients are rarely reported as they are usually detected and treated in an early state due to close clinical follow-up.

The benefit of the device for many patients (e.g. avoiding continued bleeding after acute rupture or avoiding rupture of an aneurysm with subsequent increased mortality) outweighs the risk of single events such as stent fractures or endoleak type III that could potentially lead to death in an acute or post-intervention phase. Furthermore, patients with "grafted" aneurysms are automatically included

for clinical follow-up at several time points in order to check for any problems requiring reintervention or other measures.

Furthermore, the clinical evaluation found that according to one publication by Anton et al., the endovascular treatment of true and false visceral artery aneurysms by use of the E-ventus stent graft is safe and effective.

- **Post-market Surveillance & Post-market Clinical Investigation**

The current frequencies of stent fracture or endoleak type IIId due to off-label use for the initial and modified stent graft design of the E-ventus BX Peripheral Stent Graft System are summarized below, with each affected stent graft evaluated (as of July 31, 2020).

Table 2: Reported cases of endoleaks type IIId or stent graft fractures due to off-label use from first placement on the market until July 31, 2020

	Stent Fracture [%]	Leakage [%]
Initial	0,22	0,28
Modified	0,12	0,06
Total	0,14	0,10

The above table indicates that the implemented actions from the above-mentioned CAPA in 2015 have significantly reduced the occurrence of stent fractures and endoleaks type IIId and thus were effective.

Furthermore, JOTEC GmbH is currently conducting three observational, prospective, non-randomized, multicenter studies in which peripheral covered stents are used off-label as bridging stents. The E-ventus BX peripheral stent graft system is among multiple peripheral stents from JOTEC GmbH, W. L. Gore & Associates GmbH, Bard Peripheral Vascular Inc., Getinge AB and Bentley InnoMed GmbH which are used to bridge the side branches of the stent grafts under evaluation with the intended anatomic structures. In all three studies the treatment of the patient is at the discretion of the physician and the patient. Participating physicians are asked to provide their observations collected during routine care by transferring the clinical data from the patient file into the eCRF.

A preliminary analysis of the gathered clinical data from these ongoing studies suggests that the rate of stent fractures and endoleaks type IIId that are related to the E-ventus BX used as bridging stents is comparable with peripheral stent grafts from other manufacturers. In total 192 E-ventus BX

were used throughout the three studies. Among these only 1 case of endoleak type IIId related to an incident of the E-ventus BX has been observed.

Conclusion

Taking the above-stated actions as well as the most recent results of the continuous post-market surveillance and post-market clinical follow-up studies of the E-ventus BX Peripheral Stent Graft System into consideration, it is safe to conclude that the product is not generally used off-label and that it is safe and performant when used according to the intended indication and is below the established intervention limits for off-label applications ("EVAR indications").

Furthermore, clinical and post-market data suggest that the off-label use by the healthcare professional does not constitute a higher probability of serious incidents such as the temporary or permanent deterioration of the patient's health or death when compared with the perioperative mortality rates of patients presenting with aortic aneurysms. Thus, the benefit of misusing the E-ventus BX as bridging stent outweighs the known residual risks.

Nevertheless, JOTEC GmbH proactively has decided to issue a Field Safety Corrective Action (FSCA) by means of a Field Safety Notice (FSN) to emphasize the risks of off-label use within the distributed countries as indicated in the attached FSCA report form. The description and justification of the planned action can be found in the following section.

Description and justification of the action

Taking into account all the above-stated clinical evidence and implemented actions to further control the residual risks related to off-label use, JOTEC GmbH concludes that the attached Field Safety Notice (Appendix 1, Urgent Field Safety Notice for E-ventus BX on Risks of Off-label Use) which emphasizes the criticality of adhering to the intended indication of the E-ventus BX Peripheral Stent Graft System to avoid potential serious incidents will be sufficient. ●

With kind regards,

[redacted]

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Transmission of this Field Safety Notice

This notice needs to be passed on all those who need to be aware within your organization.
If you have transferred products to any other organization please forward a copy of this notice to the organization and inform the contact person stated in this notice.

Please maintain awareness on this notice and resulting action until the procedure has been finished.

The national competent authority BfArM has received a copy of this notice.

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Contact person

[redacted]

T: 07471/922 570

F: 07471/922 122

[redacted]

Rev 1: September 2018
FSN Ref: VI-2020-11 FSCA Ref: Vi-2020-11

Date: 11.09.2020

Urgent Field Safety Notice
E-ventus BX Peripheral Stent Graft System

For Attention of*:Healthcare Providers

Contact details of local representative (name, e-mail, telephone, address etc.)*
This could be a distributor or local branch of the manufacturer. To be added at the appropriate stage in the different local languages

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Rev 1: September 2018
FSN Ref: VI-2020-11 FSCA Ref: VI-2020-11

Urgent Field Safety Notice (FSN)
E-ventus BX Peripheral Stent Graft System
Risk of Rupture/Endoleak Type IIId in Case of Off-label Use

	1. Information on Affected Devices*
1.	1. Device Type(s)*
	Implantable stent graft system
1.	2. Commercial name(s)
	E-ventus BX Peripheral Stent Graft System
1.	3. Unique Device Identifier(s) (UDI-DI)
	N/A
1.	4. Primary clinical purpose of device(s)*
	The E-ventus BX Peripheral Stent Graft System is indicated for intraluminal chronic placement in iliac and renal arteries for restoring and improving the patency and treating aneurysms, acute perforations, acute ruptures and fistulas.
1.	5. Device Model/Catalogue/part number(s)*
	E-ventus BX Peripheral Stent Graft System all catalogue numbers
1.	6. Affected serial or lot number range
	E-ventus BX Peripheral Stent Graft System all lot numbers

2 Reason for Field Safety Corrective Action (FSCA)*	
2.1.	1. Description of the product problem*
	None; reinforcement of the Instruction for Use.
2.2.	2. Hazard giving rise to the FSCA*
	In the device risk management JOTEC has identified that one of the potential hazards of off-label use may be a failure of the stent graft when used in combination with other products outside the defined indication. There are several potential hazardous situations to off-label use: • Stent rupture (individual stent graft or rupture into multiple pieces) • Damage to the sheathing / Endoleak type IIId
2.3.	3. Probability of problem arising
	Post-market data suggests that there is a very low chance of stent fracture or endoleak type IIId provided that healthcare professionals follow the intended purpose of the device.
2.4.	4. Predicted risk to patient/users
	In very rare cases (probability of occurrence <1%) these hazardous situations can cause the following potential harms: reintervention, aneurysm growth, aneurysm rupture or death.

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3. Type of Action to mitigate the risk*

3. 1. Action To Be Taken by the User*

☐ Identify Device ☐ Quarantine Device ☐ Return Device ☐ Destroy Device

☐ On-site device modification/inspection

☐ Follow patient management recommendations

☒ Take note of amendment/reinforcement of Instructions For Use (IFU)

☐ Other ☐ None

JOTEC has become aware by means of reported incidents of the fact that in a very small number of cases stent fractures and endoleaks type IIId may occur due to off-label use of the medical device.

In the device risk management JOTEC has identified that one of the potential hazards of off-label use may be a failure of the stent graft when used in combination with other products outside the defined indication.

There are several potential hazardous situations:

- Stent fracture (individual stent structs or fracture into multiple pieces)
- Damage to the sheathing / Endoleak type IIId

These hazardous situations can cause the following potential harms:

- Reintervention
- Aneurysm growth
- Aneurysm rupture
- Death

The current frequencies of stent fracture or endoleak type IIId due to off-label use for the initial and modified stent graft design of the E-ventus BX Peripheral Stent Graft System are summarized below, with each affected stent graft evaluated (26.100 sold units in total as of July 31, 2020).

	Stent Fracture [%]	Leakage [%]
Initial Design	0.22	0.28
Modified Design (from October 2015)	0.12	0.06
Total	0.14	0.10

The numbers suggest a positive development related to stent fractures as well as endoleaks type IIId as a result of the implemented design change in October 2015. The implemented design change has proven to be effective.

Furthermore, JOTEC is currently conducting three observational, prospective, non-randomized, multicenter studies in which peripheral covered stents are used off-label as bridging stents. The E-ventus BX Peripheral Stent Graft System is among multiple peripheral stents from JOTEC, Gore, Bard, Getinge and Bentley which are used to bridge the side branches of the stent grafts under evaluation with the intended

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	anatomic structures. In all three studies the treatment of the patient is at the discretion of the physician and the patient. Participating physicians are asked to provide their observations collected during routine care by transferring the clinical data from the patient file into the eCRF. A preliminary analysis of the gathered clinical data from these ongoing studies suggests that the rate of stent fractures and endoleaks type IIId that are related to the E-ventus BX Peripheral Stent Graft System used as bridging stents is comparable with peripheral stent grafts from other manufacturers. In total 192 E-ventus BX Peripheral Stent Graft System were used throughout the three studies. Among these only 1 case of endoleak type IIId related to the E-ventus BX Peripheral Stent Graft System has been observed. Please find attached more details on the preliminary study information in the appendix. Nevertheless, JOTEC strongly advises healthcare professionals to adhere to the intended purpose of the E-ventus BX Peripheral Stent Graft System as stated in the instructions for use and to refrain from off-label use. JOTEC cannot guarantee the safety and performance of the medical device in case of off-label use.
3.	2. Particular considerations for: Implantable device Is follow-up of patients or review of patients' previous results recommended? Yes Frequent follow-ups of patients with "grafted" aneurysms are mandatory, as this is standard procedure. Please ensure a rigid and frequent follow-up procedure with your patients particularly in case you have used the E-ventus BX Peripheral Stent Graft System beyond its indications.
3.	3. Is customer Reply Required? * No (If yes, form attached specifying deadline for return)
3.	**4. Action Being Taken by the Manufacturer** ☐ Product Removal ☐ On-site device modification/inspection ☐ Software upgrade ☐ IFU or labelling change ☐ Other ☒ None A design change as well as an update of the Instructions for Use emphasizing the risks of off-label use have already been implemented and proven to be effective. No further actions are required as of now.

	4. General Information*	
4.	1. FSN Type*	New
4.	2. Further advice or information already expected in follow-up FSN? *	No
4.	3. Manufacturer information (For contact details of local representative refer to page 1 of this FSN)	
	a. Company Name	JOTEC GmbH
	b. Address	Lotzenäcker 23, 72379 Hechingen/Germany
	c. Website address	https://www.jotec.com
4.	4. The Competent (Regulatory) Authority of your country has been informed about this communication to customers. *	
4.	5. List of attachments/appendices:	APPENDIX 7_2020.09.09 Preliminary Study Information for Field Safety Note; Attachment_FSCA Report E-ventus BX Peripheral Stent Graft System _09.09.2020
4.	6. Name/Signature	Monika Schulze, Director Quality & Safety Officer

	Transmission of this Field Safety Notice
	This notice needs to be passed on all those who need to be aware within your organisation or to any organisation where the potentially affected devices have been transferred. (As appropriate) Please transfer this notice to other organisations on which this action has an impact. (As appropriate) Please maintain awareness on this notice and resulting action for an appropriate period to ensure effectiveness of the corrective action. Please report all device-related incidents to the manufacturer, distributor or local representative, and the national Competent Authority if appropriate, as this provides important feedback..*

Note: Fields indicated by * are considered necessary for all FSNs. Others are optional.