The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

The Independent Medicines and Medical Devices Safety Review

Written Evidence

Manufacturers of Pelvic Mesh

Published December 2018

Contents

Disclaimer

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WARNING: Please be aware some evidence contains descriptions, pictures and audio of the harm suffered by individuals. Some may find this distressing.

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Thank you for your inquiry, Reference Number HFVWDH, received on 19th September 2018. To assist with your review, we have provided a number of items that are publicly available, including: product information and device descriptions, instructions for use, product brochures, and a list of clinical publications.

We are pleased to take this opportunity to provide the IMDDS an overview of Boston Scientific mesh products, which are reflected in Table 1. Boston Scientific currently manufactures and distributes synthetic mesh products which are used in the treatment of Pelvic Organ Prolapse and Stress Urinary Incontinence. The surgical procedure for these devices are minimally invasive and the devices are generally placed transvaginally utilising a delivery device.

TABLE 1: BOSTON SCIENTIFIC DEVICE MODELS

Product Code	Product Code Description	Placement Method
M0068318170	Uphold™ LITE System with Capio™ SLIM Suture Capturing Device	Transvaginal
M0068318150	Pinnacle LITE Pelvic Floor Repair Kit, Posterior with Capio SLIM Suture Capturing Device	Transvaginal
M0068402400	Polyform™ Synthetic Mesh, 10cm x 15cm	Abdominal and Transvaginal
M0068402410	Polyform™ Synthetic Mesh, 15cm x 20cm	Abdominal and Transvaginal
M0068318220	UPsylon™ Y Mesh Kit with Colpassist™ Vaginal Positioning Device Kit	Laparotomy, Laparoscopic and Robotic
M0068502000 M0068502050 M0068502110 M0068502120	Advantage™ Advantage™ Fit, Advantage™ Blue, Advantage Fit™ Blue System and Conservia™ Transvaginal, Conservia™ Transvaginal Fit Slings	Transvaginal
M0068502200 M0068502300	Conservia™ Transvaginal and Conservia™ Transvaginal Fit Delivery Device (Reusable)	Transvaginal
M0068503000 M0068503010	Lynx™ System and Lynx™ Blue System	Suprapubic
M0068504200	Conservia™ Suprapubic Delivery Device (Reusable)	
M0068504210	Conservia™ Transobturator /Suprapubic Sling*	Transobturator
M0068505200 M0068506200	Conservia™ Transobturator Curved or Halo Delivery Device (Reusable)	
M0068504000 M0068504110 M0068505000 M0068505110	Obtryx™ System and Obtryx II™ System Transobturator Sling System with PrecisionBlue™ Design (Curved or Halo Delivery Device)	
M0068507000 M0068507010	Solyx™ SIS and Solyx Blue SIS System	Single Incision and Transvaginal

*Design of mesh assembly for Conservia Transobturator & Suprapubic Sling are identical

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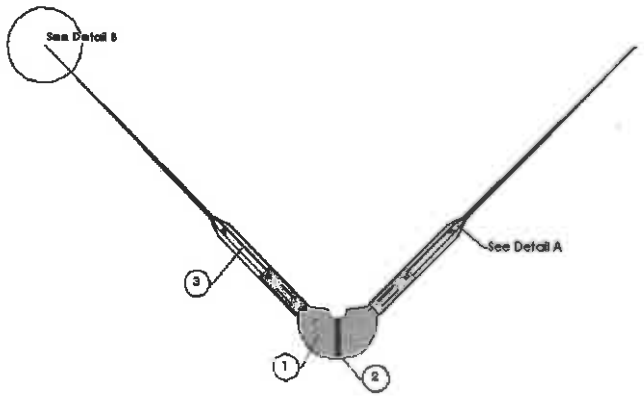
DEVICE DESCRIPTION

Uphold™ LITE

The Uphold LITE Vaginal Support System is a sterile, single use device for transvaginal placement, shown in Image 1. It consists of one pre-cut Surgical Mesh and two integrated Leg Assemblies. The polypropylene knitted surgical mesh body consists of undyed and dyed polypropylene monofilament fiber and is intended to be permanently implanted within the body for pelvic organ prolapse repair. The integrated leg assemblies include a dart/needle, lead, dilator, leader loop and a protective sleeve and are used to facilitate placement of the mesh through the sacrospinous ligament (SSL) or arcus tendineous (AT). Once the Surgical Mesh is placed, the Leg Assemblies are removed and discarded.

Image 1: Uphold LITE Mesh Assembly



1) Mesh, 2) Centre line, 3) Mesh Leg Assembly

Polyform™ Synthetic Mesh

Polyform Synthetic Mesh is a single-use synthetic mesh, constructed of knitted monofilaments of polypropylene fibres as shown in Image 2. It is intended to be utilised for surgical procedures pertaining to the pelvic floor such as tissue reinforcement and stabilisation of fascial structures of the pelvic floor in vaginal wall prolapse. Polyform Synthetic Mesh is supplied sterile and provided in sheet form to be cut to size and sutured by the surgeon to meet the individual patient's needs.

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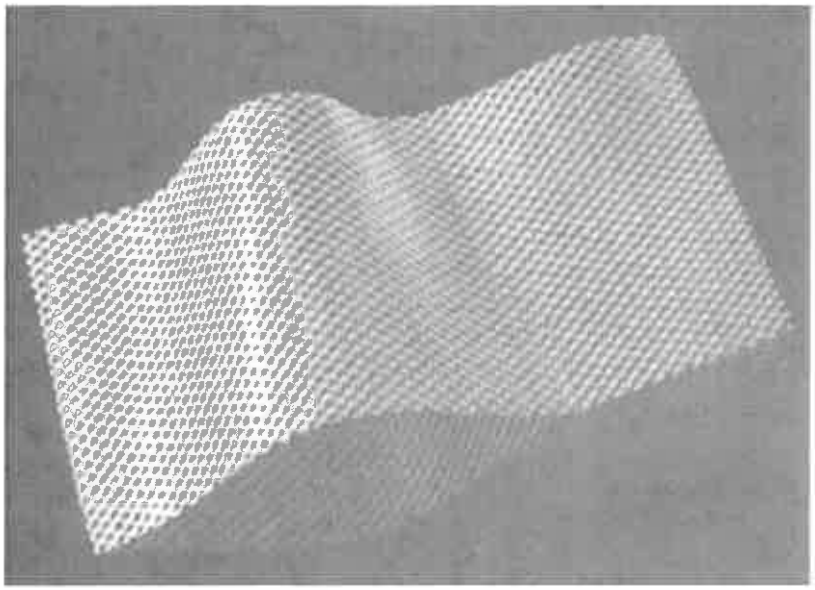
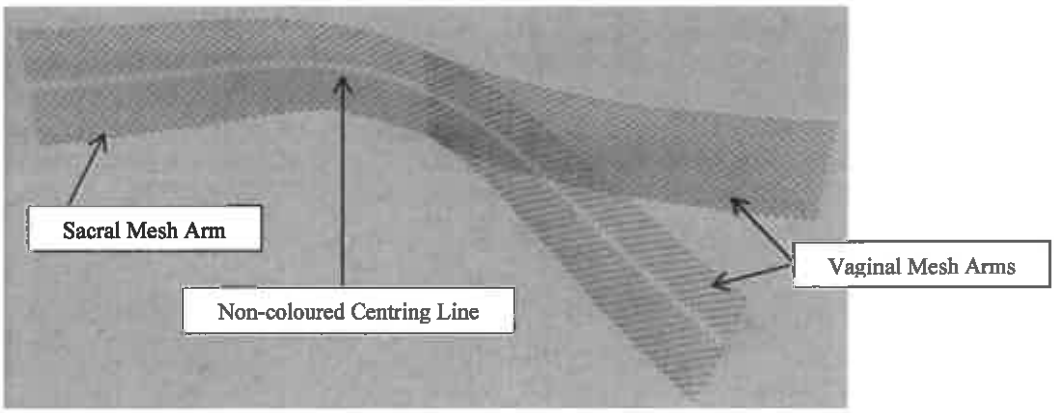
Image 2: Polyform Synthetic Mesh



UPsylon™ Y-Mesh

UPsylon Y Mesh is a preformed Y-shaped, lightweight polypropylene mesh consisting of two vaginal mesh arms and one sacral mesh arm as shown in Image 3. The Upsylon Y Mesh is blue in colour with a non-coloured centring line. Upsylon Y Mesh is intended for use as a bridging material for sacrocolposuspension / sacrocolpopexy in surgical treatment of vaginal vault prolapse. The single-use sterile mesh is introduced via laparotomy, laparoscopic or robotic approach and user supplied sutures are used to secure the Upsylon Y mesh in place to the sacrum and vaginal walls.

Image 3: Upsylon Y-Mesh



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Advantage™ System, Advantage Fit™ System, Advantage Blue System, & Advantage Fit Blue System

The Advantage System, Advantage Fit System, Advantage Blue System and Advantage Fit Blue System are sterile, single use systems, consisting of one (1) delivery device and one (1) mesh assembly. Each mesh assembly is comprised of a polypropylene knitted mesh protected by a disposable plastic sleeve. At the distal ends of the mesh assembly are two dilators designed to be placed over the needle end of the delivery device. The disposable delivery device consists of a handle with a curved needle, and a pusher component. The delivery device is designed to facilitate the passage of the mesh assembly through bodily tissues for transvaginal placement.

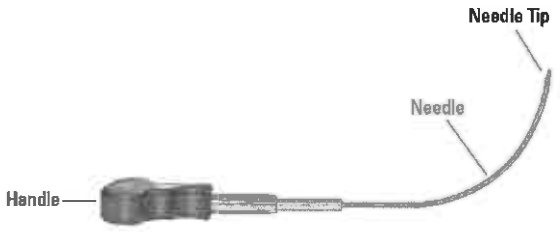
Conservia Transvaginal and Transvaginal Fit Sling

The Conservia Transvaginal (TV) and Transvaginal (TV) Fit Mid-Urethral Slings are sterile, single use mesh assemblies. Each mesh assembly is comprised of a polypropylene knitted mesh protected by a disposable plastic sleeve. At the distal ends of the mesh assembly are two dilators designed to be placed over the needle end of the delivery device. The design of the mesh assembly is identical to that of the Advantage and Advantage Fit mesh assembly.

Conservia Transvaginal and Transvaginal Fit Delivery Devices

The Conservia Delivery Devices are reuseable and sold separately from the Conservia Mid Urethral Sling. The Conservia Transvaginal and Transvaginal Fit reusable Delivery Devices consist of one (1) Delivery Device. Both Delivery Devices consist of a handle with a curved stainless steel needle as shown in Image 4. Although very similar in design the difference in these models is the diameter, length and curvature of the needle dimensions. These Delivery Devices are sold separately and designed to be used with the Conservia Transvaginal and Conservia Transvaginal Fit Mid-Urethral Slings which facilitate the passage of the mesh assembly through bodily tissues for transvaginal placement.

Image 4: Conservia TV & TV Fit Delivery Device



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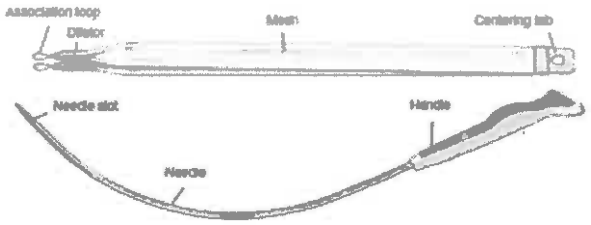
Lynx™ System & Lynx Blue System

The Lynx and Lynx Blue Systems are sterile, single use systems each consisting of two (2) delivery devices and one (1) mesh assembly as shown in Image 5. The mesh assembly is comprised of a polypropylene knitted mesh protected by a disposable plastic sleeve. At the distal ends of the mesh assembly there are association loops designed to be placed in the needle slot of the distal end of the delivery device. The disposable delivery device consists of a handle with a curved needle. The needle is designed to facilitate the passage of the mesh assembly through bodily tissues for suprapubic placement.

Image 5: Lynx & Lynx Blue System



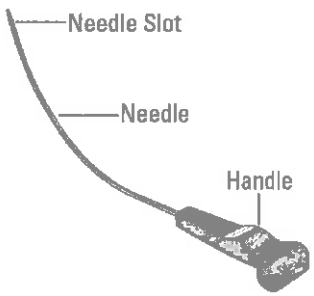
Conservia Transobturator /Suprapubic Sling

The Conservia Transobturator /Suprapubic Sling are sterile, single use mesh assemblies. Each mesh assembly is comprised of a polypropylene knitted mesh protected by a disposable plastic sleeve. At the distal ends of the mesh assembly there are association loops designed to be placed in the needle slot of the distal end of the delivery device. The design of the mesh assembly is identical to that of the Lynx/Obtryx mesh assembly.

Conservia Suprapubic Delivery Devices

The Conservia Suprapubic reusable Delivery Devices consist of two (2) Delivery Devices. The Delivery Devices are reusable devices consisting of a handle with a stainless steel needle as shown in Image 6. The reusable Delivery Devices are sold separately and designed to be used with the Conservia Transobturator/Suprapubic Mid-Urethral Sling which facilitates the passage of the mesh assembly through bodily tissues for suprapubic placement.

Image 6: Conservia Suprapubic Delivery Device



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Conservia Transobturator Curved or Halo Delivery Devices

The Conservia Transobturator Curved and Halo reusable Delivery Devices each consist of two (2) Delivery Devices. The Delivery Devices are reusable devices consisting of a handle with a stainless steel needle as shown in Images 7 and 8. Both Halo and Curved reusable Delivery Device designs are to be used with the Conservia Transobturator /Suprapubic Mid-Urethral Sling which facilitates the passage of the mesh assembly through bodily tissues for placement through the obturator foramen.

Image 7: Conservia Transobturator- Curved Delivery Device

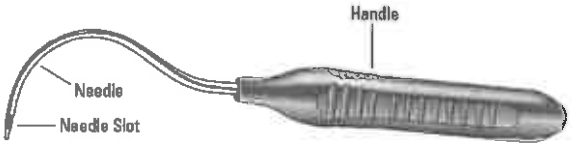
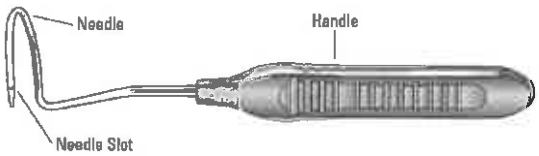


Image 8: Conservia Transobturator- Halo Delivery Device



Obtryx™ System (Curved or Halo)

The Obtryx Sling System – Curved or Halo are sterile, single use system consisting of two (2) delivery devices and one (1) mesh assembly as shown in Images 9 and 10. The mesh assembly is comprised of a polypropylene knitted mesh protected by a disposable plastic sleeve. At the distal ends of the mesh assembly there are association loops designed to be placed in the needle slot of the distal end of the delivery device. The disposable delivery devices consist of a handle with a stainless steel needle. The needle is designed to facilitate the passage of the mesh assembly through bodily tissues for placement through the obturator foramen.

Image 9: Obtryx Curved System

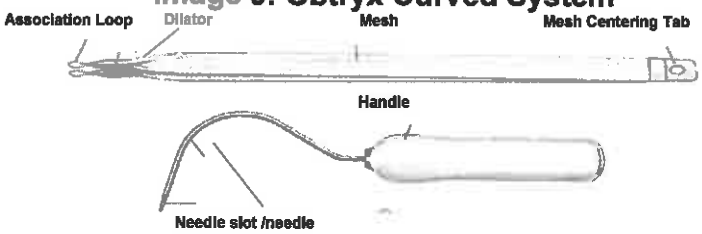


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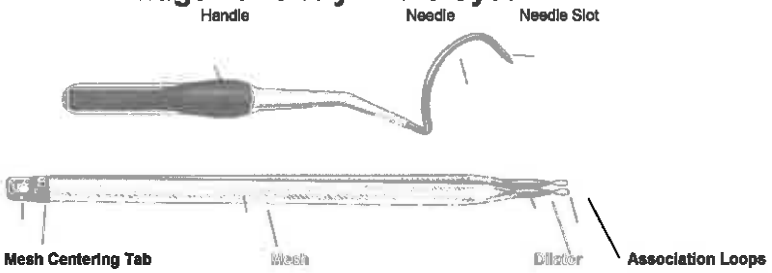
Image 10: Obtryx Halo System



Obtryx II™ System Transobturator Sling System with PrecisionBlue™ Design (Curved or Halo)

The Obtryx II Sling Systems – Curved or Halo are sterile, single use system consisting of two (2) delivery devices one (1) mesh assembly as shown in Images 11 and 12. The mesh assembly consists of blue polypropylene knitted mesh, dilator legs with association loops, protective sleeves, leader loops, a centre tab and centre tab lead. At the distal ends of the dilator legs there are association loops designed to be placed in the needle slot of the distal end of the delivery device. The disposable delivery devices consist of a handle with a stainless steel needle. The needle is designed to facilitate the passage of the mesh assembly through bodily tissues for placement through the obturator foramen.

Image 11: Obtryx II Curved System

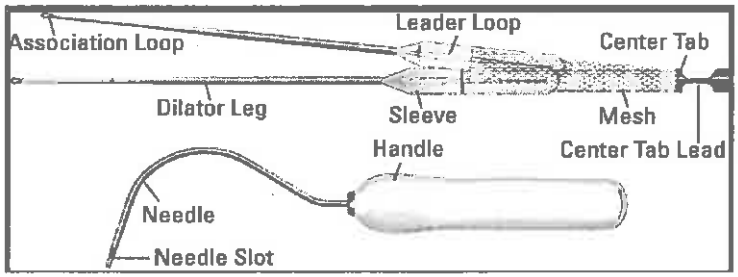
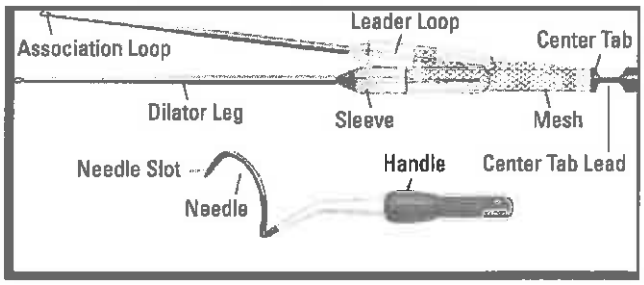


Image 12: Obtryx II Halo System



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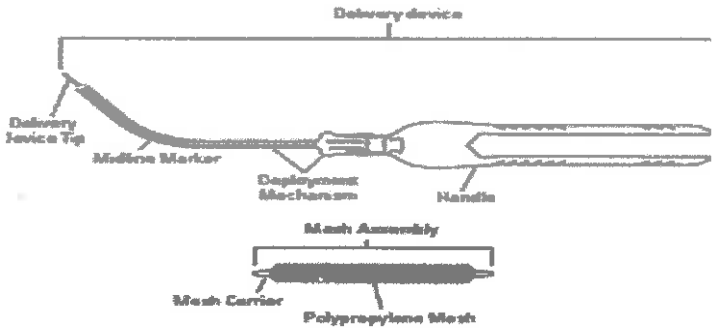
Solyx™ SIS System & Solyx Blue SIS System

The Solyx and Solyx Blue SIS (Single Incision Sling) Systems are sterile single use systems each consisting of one (1) delivery device and one (1) mesh assembly as shown in Image 13. The mesh assembly is comprised of a polypropylene knitted mesh with polypropylene carriers at each end of the distal mesh. The carrier is designed to be placed on the tip of the delivery device. The disposable delivery device consists of a handle, a stainless steel shaft and a deployment mechanism. The delivery device is designed to facilitate the passage of the mesh assembly through bodily tissues for placement into the obturator internus muscle.

Image 13: Solyx & Solyx Blue SIS System



INSTRUCTIONS FOR USE

Please refer to Appendix A for Instructions for Use.

PRODUCT BROCHURE

Please refer to Appendix B for Product Brochures.

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PUBLISHED LITERATURE SUPPORT

Stress Urinary Incontinence (SUI)

Surgical treatment with a synthetic mesh sling is considered the gold standard for women with ongoing SUI. Generally, conservative management strategies such as lifestyle changes, physical therapy, scheduled voiding regimes, and behavioural therapies are the first line of treatment, but offer varying rates of success and can negatively impact daily routines and quality of life.

Table 2 is a non-exhastive list of documented publications where Boston Scientific's mesh sling systems have been used.

TABLE 2 – PUBLISHED LITERATURE SUPPORT – SUI

Article Author and Year of Publication
Advantage™ System
Chevrot A, et al. Long-term efficacy and safety of tension free vaginal tape in a historic cohort of 463 women with stress urinary incontinence Int Urogynecol J. 2017
Balachandran A, et al. Does the diagnosis of detrusor overactivity affect the long-term prognosis of patients treated with a retropubic midurethral sling? Int Urogynecol J. 2016
Basu M, et al. Three-year results from a randomised trial of a retropubic mid-urethral sling vs the Miniarc single incision sling for SUI Int Urogynecol J. 2013
Renganathan A, et al. A series of advantage suburethral slings J Obstet Gynaecol. 2011
Basu M, et al. A randomised trial of a retropubic tension-free vaginal tape versus a mini-sling for stress incontinence BJOG. 2010
Lim YN, et al. Do the Advantage slings work as well as the tension-free vaginal tapes? Int Urogynecol J. 2010
Moalli PA, et al. Tensile properties of five commonly used mid-urethral slings relative to the tvt™ Int Urogynecol J Pelvic Floor Dysfunct. 2008
Advantage™ System/Obtryx™ System
Brennand EA, et al. Five years after midurethral sling surgery for stress incontinence: obesity continues to have an impact on outcomes Int Urogynecol J. 2017
Ross S, et al. Transobturator tape versus retropubic tension-free vaginal tape for stress urinary incontinence: 5-year safety and effectiveness outcomes following a randomised trial Int Urogynecol J. 2016
Brennand EA, et al. Twelve-month outcomes following midurethral sling procedures for stress incontinence: impact of obesity BJOG. 2015
Tarcan T, et al. Safety and efficacy of retropubic or transobturator midurethral slings in a randomized cohort of Turkish women Urol Int. 2014
Arunkalaivanan A, et al. Efficacy and safety of transobturator tape (Obtryx) in women with stress urinary incontinence and intrinsic sphincter deficiency: Results from International Obtryx Registry ICS Meeting 2010
Costa P. Comparisons of safety and efficacy of the Obtryx® Sling and Advantage™ Mid-Urethral Sling for the treatment of stress urinary incontinence: Propensity matching results in a large international registry AAGL 2010
Cholhan HJ, et al. Dyspareunia associated with paraurethral banding in the transobturator sling Am J Obstet Gynecol. 2010
Ross S, et al. Transobturator tape compared with tension-free vaginal tape for stress incontinence: a randomized controlled trial Obstet Gynecol. 2010

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Robert M, et al. Patient expectations, subjective improvement and objective cure: Is there a difference between the transobturator tape and the tension free vaginal tape procedure? Neurourology and Urodynamics 2009
Costa P. Safety of sub-mid urethral tapes: Report on 3 and 12 months follow-up on 1198 patients in an international registry J Urol. 2008
Costa P. Results of retropubic and transobturator placement of sub-mid urethral tapes (M.U.T.) in first international registry: Results on 984 patients at 3 and 12 months ICS 2007
Costa P. First international registry on sub-mid urethral tapes (M.U.T.) implanted by retro pubic of trans-obturator route: Preliminary results on 700 patients EAU 2007
Obtryx™ System
Aygül C, et al. Evaluation of the efficacy of transobturator tape surgery in the treatment of stress urinary incontinence using urodynamics and questionnaires Turk J Obstet Gynecol. 2016
Hogston P, et al. Medium term follow-up of women who underwent transobturator suburethral tape insertion for the treatment of urinary stress incontinence BJOG. 2013
Smith P, et al. Comparison of single-incision mid-urethral tape (Ophira™) and transobturator tape (Obtryx™) suburethral sling procedures for female stress urinary incontinence J Clin Med and Research 2013
May J, et al. Outcome of Obtryx Transobturator Sling for stress incontinence in Scottish women Int Journal Gynecol Obstet. 2012
Hogston P. Single surgeon experience with 125 transobturator sling procedures Int Urogynecol J./IUGA 2011 Wilson C, et al. Short-term efficacy of a transobturator sling in women veterans with a history of sexual trauma MAAUA 2010
Litwiller SE. Long term efficacy and safety of the Obtryx Sling (Boston Scientific Corp.) for treatment of stress urinary incontinence in a community setting: an analysis of outcomes and quality of life. J Pelvic Med Surg. 2009
Tahseen S, et al. Effect of transobturator tape on overactive bladder symptoms and urge urinary incontinence in women with mixed urinary incontinence Obstet Gynecol./MAAUA 2009
Dati S. Obtryx System: Transobturator out-in sling in the treatment of isolated or POP-associated urinary incontinence Int Urogynecol J. 2007
Lynx™ System
Agarwala N. A randomized comparison of two synthetic mid-urethral tension-free slings UroToday International Journal 2008
Noblett KL, et al. Lynx midurethral sling system: a 1-year prospective study on efficacy and safety Int Urogynecol J Pelvic Floor Dysfunct. 2008
Solyx™ (Single-Incision Sling System)
Serels S, et al. Long term follow up of the Solyx Single Incision Sling in the treatment of female stress urinary incontinence (SUI) Open Journal of Urology 2014
Serels S, et al. Safety and efficacy of the Solyx Single Incision Sling System for the treatment of SUI: Preliminary results UroToday International Journal 2011
Serels S, et al. Preliminary findings with the Solyx™ single-incision sling system in female stress urinary incontinence Int Urogynecol J. 2010

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Pelvic Organ Prolapse (POP)

Surgical treatment with synthetic mesh to treat pelvic organ prolapse is typically performed with the goal of restoring organs to their original location in women whose own tissues are not strong enough for native tissue repair. Some types of surgical mesh are placed through an incision in the vagina. Others are done through an incision in the abdomen or with laparoscopy.

Table 3 is a non-exhaustive list of documented publications where Boston Scientific's synthetic mesh to treat pelvic organ prolapse have been used.

TABLE 3 – PUBLISHED LITERATURE SUPPORT – POP

Article Author and Year of Publication
Uphold™ LITE
Rahkola-Soisalo P, Mikkola TS, Altman D, Falconer C. Pelvic Organ Prolapse Repair Using the Uphold Vaginal Support System: 5-Year Follow-up. Female Pelvic Medicine and Reconstructive Surgery. 2017 Epub Before print.
Gutman RE, Rardin CR, Sokol ER, Matthews C, Park AJ, Iglesia CB, Geoffrion R, Sokol AI, Karram M, Cundiff GW, Blomquist JL, Barber MD. Vaginal and laproscopic mesh hysteropexy for uterovaginal prolapse: a parallel cohort study. Am J Obstet Gynecol. 2017 Jan; 216(1):38. e1-38. e11.
Letouzey V, Ulrich D, Balenbois E, Cornille A, de Tayrac R, Fatton B. Utero-vaginal suspension using bilateral vaginal anterior sacrospinous fixation with mesh: intermediate results of a cohort study. Int Urogynecol J. 2015 Dec;26(12):1803-7.
Vu MK, Letko J, Jirschele K, Gafni-Kane A, Nguyen A, Du H, Goldberg RP. Minimal mesh repair for apical and anterior prolapse: initial anatomical and subjective outcomes. Int Urogynecol J. 2012 Dec;23(12):1753-61.
Jirschele K, Seitz M, Zhou Y, Rosenblatt P, Culligan P, Sand P. A multicenter, prospective trial to evaluate mesh-augmented sacrospinous hysteropexy for uterovaginal prolapse. Int Urogynecol J. 2015 May; 26(5):743-8.
Altman D, Moøller Bek K, Mikkola T, Gunnarsson J, Ellström Engh M, Falconer C. Intra-and perioperative morbidity following pelvic organ prolapse repair using a transvaginal suture capturing mesh device compared to trocar guided transvaginal mesh and traditional colporrhaphy [abstract]. Neurourol Urodyn. 2013; 32 (6): 873-4. 43rd Annual Meeting of the International Continence Society, ICS 2013 Barcelona, Spain 2013-08-26 to 2013-08-30

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POST-MARKET CLINICAL TRIAL SUPPORT

Boston Scientific is conducting two post-market clinical studies in the United States. Information pertaining to the study design and current status of each can be viewed at the ClinicalTrials.gov website using the NCT identifier as shown in Table 4.

TABLE 4 – POST-MARKET CLINICAL STUDIES SPONSORED BY BOSTON SCIENTIFIC

ClinicalTrials.gov Identifier	Study Title	Study Status
NCT01784588	A Prospective, Non-Randomized, Parallel Cohort, Multi-center Study of the Solyx™ Single Incision Sling System vs. the Obtryx™ II Sling System for the Treatment of Women With Stress Urinary Incontinence	Completed
NCT01917968	A Prospective, Non-Randomized, Parallel Cohort, Multi-center Study of Uphold LITE Versus Native Tissue for the Treatment of Women With Anterior/Apical Pelvic Organ Prolapse	Active, enrollment complete

In addition to the above referenced post-market clinical studies, Boston Scientific is a collaborator in a National Institute of Child Health and Human Development (NICHD) sponsored clinical study, also known as the SUPeR study (Study of Uterine Prolapse Procedures - Randomized Trial). Information pertaining to the study design and current status can be viewed at the ClinicalTrials.gov website using the NCT identifier as shown in Table 5.

TABLE 5 – POST-MAREKT CLINICAL STUDY SPONSORED BY NICHD

ClinicalTrials.gov Identifier	Study Title	Study Status
NCT01802281	A Randomized Trial of Vaginal Surgery for Uterovaginal Prolapse: Vaginal Hysterectomy With Native Tissue Vault Suspension vs. Mesh Hysteropexy Suspension Study of Uterine Prolapse Procedures - Randomized Trial (SUPeR)	Active, enrollment complete

BOSTON SCIENTIFIC APPENDICES

APPENDIX A

Instructions for Use for the devices listed in Table 1, except:

- Pinnacle LITE Pelvic Floor Repeat Kit, Posterior with Capio SLIM Suture Capturing Device

APPENDIX B

Examples of product Brochures for the devices listed in Table 1, including:

Capio™ SLIM:

http://www.bostonscientific.com/content/dam/bostonscientific/uro-wh/portfolio-group/pelvic-floor-reconstruction/suturing-systems/capio-slim/pdf/capio-slim-brochure.pdf

Lynx™ Sling and Blue Sling System:
https://www.bostonscientific.com/content/dam/bostonscientific/uro-wh/portfolio-group/sling-systems/blueMesh/pdf/us/lynx-brochure-US.pdf

Obtryx™ II:

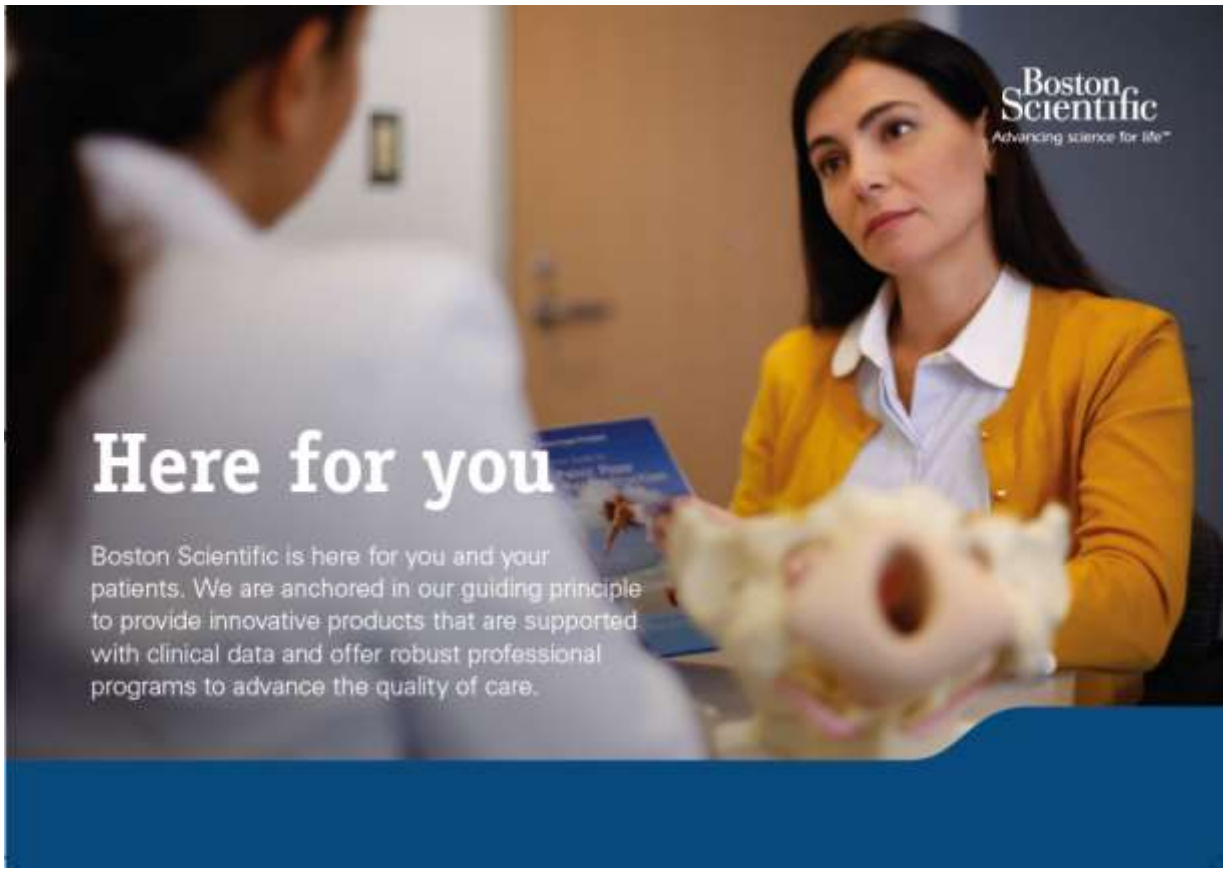
http://www.bostonscientific.com/content/dam/bostonscientific/uro-wh/portfolio-group/sling-systems/obtryx-II/Obtryx_II_Brochure_A4_WH_118616_AD_AUG_2017_DINURO2283EA_English.pdf

Additional:

Xenform™ Soft Tissue Repair Matrix

http://www.bostonscientific.com/content/dam/bostonscientific/uro-wh/portfolio-group/pelvic-floor-reconstruction/xenform/pdfs/WH-551002-AA_Xenform_POP_Patient_Brochure_English_DINURO2303EA_Preview.pdf

Here for You Brochure:



PRODUCT INNOVATION

Boston Scientific is committed to developing new products, improving existing product lines and exploring new, innovative ways to treat pelvic floor disease and related areas.

Recent innovations

- Upsylon™ YMesh and Cotrasset™ Vaginal Positioning Device
- Obtryx™ II Sling System
- Capio™ SLIM Suture Capturing Device
- Uphold™ LITE Vaginal Support System w/ Capio™ SLIM Suture Capturing Device

Breadth of options for evolving algorithms

- **POP**: Native tissue fixation, biologic grafts (xenograft and allograft) and lightweight, low surface area mesh for both transvaginal augmentation and SCF
- **SUI**: Retropubic, suprapubic, transobturator and single-incision slings

CLINICAL EXCELLENCE

Boston Scientific is committed to supporting evidence-based medicine through sponsoring and funding women's health research worldwide for the treatment of female SUI and POP.

Participation in three 522 trials

Uphold™ LITE Vaginal Support System
- NIH Uphold System Study (i.e. SUPeR) – the first POP study to be initiated. Enrollment is complete with 180 patients enrolled at 9 sites across the U.S.

Solys™ SIS /Obtryx™ II Sling Systems
- Enrollment complete with 276 patients enrolled at 21 sites

Xenform™ Soft Tissue Matrix
- Enrollment is ongoing with 430+ patients across 23 sites

Supporting evidence-based medicine

- 13 POP studies covering SSLF, hysteropexy and transvaginal augmentation with mesh and biologic grafts
- 2 recent SUI studies including both TOT and SIS sling approaches

ROBUST PROFESSIONAL PROGRAMMES

Boston Scientific is committed to helping you and your patients advance knowledge around disease states and treatment options.

Advancing knowledge with surgeons and patients

- Supported over 80+ patient education events (Break Free From PFD's) as part of the PFD Alliance with AUGS

Physician training & cadaver labs

- 40 educational events in 2015
- 9 cadaver courses, 159 attendees
- Over 270 physicians trained

Pelvic Floor Institute™ website

- 1200 visitors in 2015
- 7833 total visits
- 186 hours/month avg

Boston Scientific
Advancing science for life™

Patient Guide to Understanding Stress Urinary Incontinence

https://www.bostonscientific.com/content/dam/bostonscientific/uro-wh/portfolio-group/health-conditions/stress-urinary-incontinence/SUI-Patient-Brochure.pdf

Pelvic Floor Clinical Support Document:

https://www.bostonscientific.com/content/dam/bostonscientific/uro-wh/sites/pfi/shared/pdfs/pelvic_floor_clinical_support_brochure.pdf

Women's Health Brochure:

http://www.bostonscientific.com/content/dam/bostonscientific/uro-wh/portfolio-group/pelvic-floor-reconstruction/general/WH-Portfolio-Brochure.pdf

Submission from ETHICON

Introductory Request	Please confirm that you give permission for that evidence to be used for the purposes of the Review. Any information you choose to provide will be held according to information handling policies which are available on our website, 'How we handle the Information you provide to the Review – Data Protection and Privacy Information' and the 'Anonymity and Redaction Framework'.

Noted and approved, subject to your compliance with the requirements and obligations of the Data Protection Act and the General Data Protection Regulation.

Question	1. Please confirm the synthetic mesh products that you market or have previously marketed within the EU for use in urogynaecological surgery.

Stress Urinary Incontinence ("SUI") Products:

Gynecare TVT™ (*Tension-free Vaginal Tape*)
Gynecare TVT™ with Abdominal Guides
Gynecare TVT-O™
Gynecare TVT-Secur™
Gynecare TVT-Abbrevo™
Gynecare TVT-Exact™

Pelvic Organ Prolapse ("POP") Products:

Gynecare Gynemesh PS™
Gynecare Prolift™
Gynecare Prosima™
Gynecare Prolift +M™
Gynecare Gynemesh M™
Artisyn™ Y-shaped Mesh

Question	2. Please detail for each such device: a) Premarket testing undertaken; b) any clinical evaluation undertaken; c) whether conformity was declared on the basis of equivalence to an exisiting device, and if so, please detail the existing device; d) specify the notified body used for the conformity assessment, and the date the conformity assessment was undertaken; e) date of CE marking; f) any changes to the design; g) any changes to the indications (please detail);

Please refer to **Attachment 1** for the Ethicon SUI mesh products and **Attachment 2** for the Ethicon POP mesh products for responses to 2(a) to (g), 5 and 8.

Question	2. Please detail for each such device: h) date of removal from market in the UK and worldwide if applicable, and reasons for this;

In May 2012 Ethicon made the decision to discontinue the following products:

- Gynecare Prosima Pelvic Floor Repair System
- Gynecare Prolift Systems
- Gynecare Gynemesh M
- Gynecare Prolift +M Pelvic Floor Repair System
- Gynecare TVT Secur System

The decision to cease worldwide distribution of the products was a business decision made on the basis of commercial viability of the products and decline in the worldwide market and was not related to the safety or efficacy of the devices.

The precise date on which sales of the products ceased varied from market to market and within markets and depended on factors which included existing tender commitments. In general terms the de-commercialisation process in the EU (including the UK) began in Q1 2013 and was intended to be complete by the end of the year.

As this was not a product recall and was not driven by safety concerns, Ethicon informed customers that they were able to continue using any product(s) in their hospital(s) beyond the date of discontinuance, provided that the individual units were not expired.

Question	2. Please detail for each such device: i) if the device continued to be marketed elsewhere in the world.

As explained above, the precise dates varied between markets and indeed within markets. Whilst the discontinuance had global effect, it is impractical to identify the precise dates on which the marketing of the products ended elsewhere in the world.

Question	3. Can you describe the marketing strategy for each device and provide examples of the marketing literature used? For each device, please can you include any instructions for use including details of changes over time.

Ethicon stopped actively marketing the available products in 2016.

Prior to this, the products were marketed to experienced pelvic floor surgeons who regularly undertook pelvic floor surgery and/or incontinence surgery.

A core part of the marketing strategy was to use extensively trained field sales operatives to speak directly to surgeons. The sales operatives used a range of sales aids to market the products including information leaflets explaining the products to the surgeons and their IFUs (instructions for use). Sales operatives also shared published clinical data and testimonials from other clinicians. All of the sales aids were passed through a copy approval process, where draft materials were reviewed by regulatory affairs, medical affairs and communications.

The company also exhibited the products at national and local surgical symposiums, congresses and events intended for pelvic floor surgeons.

Please find examples of marketing literature in **Attachment 3**.

The current Instructions For Use (IFU) for devices still marketed, and the final IFUs for devices no longer marketed are included at **Attachment 4** to this response.

Ethicon anticipates that it will be able to provide the review with details of changes to the IFUs within the next few weeks.

Question	4. Please provide details of device traceability for example Unique Device Identifiers, shelf life and reason(s) for that shelf life, batch traceability, and batch and product recall.

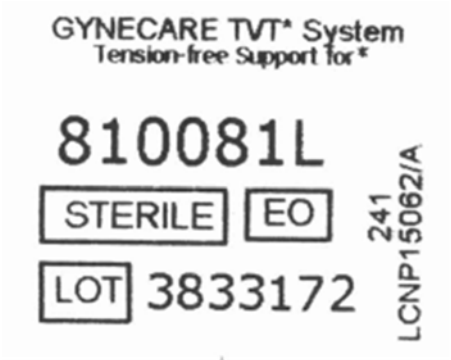
Each individual product packaging includes a device identifier in the form of a product label (example below), that contains:

- The name of the product in words;

Question	4. Please provide details of device traceability for example Unique Device Identifiers, shelf life and reason(s) for that shelf life, batch traceability, and batch and product recall.

- The Product code, which identifies the product (example 810081L);
- "LOT" – this is the Lot number, otherwise known as a batch code, (example 3833172), which identifies the specific manufacturing batch of the particular product. It enables Ethicon to:
    - identify the specific date and place of manufacture of the batch in question;
    - match up all quality control records applicable to that particular batch; and
    - identify when the product left Ethicon and to whom it was supplied (as explained below, if provided with the Lot number, Ethicon can identify the entity to which it supplied the product, e.g. a particular NHS Health Trust or private hospital);
- Icon: "STERILE EO". This symbol confirms that the product was sterilized by ethylene oxide;
- The product label itself is in the form of a "sticky" label and is designed so that it can be peeled off and affixed by the surgical staff onto the patient's medical records for future identification.

See example of a product label:



In addition, the packaging of the product clearly states the Use By date (i.e. the maximum "shelf life" of the product). The reason for providing the maximum shelf life is to ensure that the product is not used (implanted) on a date beyond the period when it remains sterilized.

Once Ethicon is provided with the Lot number, Ethicon can identify the manufacturing details associated with the specific product implanted in a patient, the identity of whom is otherwise unknown to Ethicon for patient confidentiality reasons. As indicated above, Ethicon can identify any product from the details contained in the product label which is provided so it can be affixed to a patient's medical records, as well as the date and place of manufacture and the date it was shipped and the entity to which it was supplied by Ethicon.

In the event that Ethicon took the decision to undertake a batch or full product recall, it could recall batches by Lot number as appropriate. Hospitals then would be responsible to identify the patients impacted, if any, since Ethicon does not have patient contact information for patient confidentiality reasons.

Question	5. Please share any evidence of positive feedback on pelvic mesh from clinicians or patient groups.

Please refer to **Attachment 1** for the Ethicon SUI mesh products and **Attachment 2** for the Ethicon POP mesh products for responses to 2(a) to (g), 5 and 8.

Question	6. For each device, please specify the composition of the materials and changes over time.

All of Ethicon's pelvic mesh products contain Prolene™ based mesh.

Prolene is the patented proprietary name of a non-absorbable synthetic monofilament made from polypropylene which is treated with a proprietary antioxidant package and sourced exclusively from the USA.

Prolene was first determined to be safe and effective for use in Prolene polypropylene nonabsorbable surgical sutures in 1969.

<u>The Gynecare TVT Family of Products</u>

The Gynecare TVT family of products consists of:

- Gynecare TVT Tension-free Vaginal Tape System
- Gynecare TVT Obturator System
- Gynecare TVT Secur System
- Gynecare TVT Abbrevo Continence System
- Gynecare TVT Exact Continence System

The mesh used in the Gynecare TVT family of products is Prolene Mesh. Prolene Mesh is constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in Prolene polypropylene nonabsorbable surgical suture. Prolene Mesh is knitted by a process which interlinks each fibre junction.

TVT Secur also contained two centimeter absorbable fixation tips of fleece-like material made from Vicryl™ (polyglactin 910) and PDS™ (poly-p-dioxanone) suture yarn which sandwiched the end sections of the Prolene Mesh. These coated ends were added to facilitate passage and placement of the mesh implant and were then absorbed.

The composition of the Prolene Mesh used in the Gynecare TVT family of products has not changed over time.

<u>Gynecare Gynemesh PS Nonabsorbable Prolene Soft Mesh</u>

Gynecare Gynemesh PS Nonabsorbable Prolene Soft Mesh is constructed of knitted filaments of extruded polypropylene identical in composition to Prolene Polypropylene Suture, Nonabsorbable Surgical Suture. The mesh is constructed of reduced diameter monofilament fibres.

The composition of Gynecare Gynemesh PS Nonabsorbable Prolene Soft Mesh has not changed over time.

Gynecare Prolift Pelvic Floor Repair Systems

The Gynecare Prolift Total, Anterior and Posterior Pelvic Floor Repair Systems contained pre-cut Gynecare Gynemesh PS Nonabsorbable Prolene Soft Mesh.

Gynecare Prosima Pelvic Floor Repair Systems

The Gynecare Prosima Anterior, Posterior and Combined Pelvic Floor Repair Systems contained pre-cut Gynecare Gynemesh PS Nonabsorbable Prolene Soft Mesh.

Gynecare Gynemesh M Partially Absorbable Mesh

Gynecare Gynemesh M Partially Absorbable Mesh was constructed of knitted filaments of extruded polypropylene and poliglecaprone-25 identical in composition to Prolene Polypropylenes Suture, as well as and Monocryl™ (poliglecaprone-25) Suture. Monocryl is prepared from a copolymer of glycolide and epsilon-caprolactone.

The composition of Gynecare Gynemesh M Partially Absorbable Mesh has not changed over time.

Gynecare Prolift +M Pelvic Floor Repair Systems

The Gynecare Prolift +M Total, Anterior and Posterior Pelvic Floor Repair Systems contained pre-cut Gynecare Gynemesh M Partially Absorbable Mesh.

Artisyn Y-Shaped Mesh

Artisyn Y-Shaped Mesh contains pre-cut Gynecare Gynemesh M Partially Absorbable Mesh.

Question	7. Please can you provide sales data for each device, and if known, market share.

This request calls for production of commercially sensitive information as to sales data, which the company is not obliged to disclose.

Question	8. Please provide details of any post-marketing vigilance studies of relevance to the Review, including 522 studies if appropriate.

Please refer to **Attachment 1** for the Ethicon SUI mesh products and **Attachment 2** for the Ethicon POP mesh products for responses to 2(a) to (g), 5 and 8.

Question	9. Please can you supply a summary of in-vivo shrinkage data relevant to your products.

While you have asked for in-vivo shrinkage data, it should be noted that the mesh in Ethicon's TVT and POP devices itself does not shrink. Instead, the macroporous Ethicon meshes allow for the integration of the patient's tissue through the mesh (by design) which naturally forms scar tissue. During wound healing and scar formation, the tissues may contract whether or not mesh is present.

The outcomes with Ethicon's TVT products are favorable as compared to native tissue repair as discussed in responses to Questions 5 and 8 and do not support that significant tissue contraction occurs. Further, placement of the TVT sling is carried out utilizing a very small incision and the sling does not reside in the vagina. This technique and the design of the TVT devices leads to very little if any vaginal scarring, and therefor tissue contraction, as the midline incision is small and heals. Dissection is also less than that needed for the native tissue abdominal procedures that have much larger incisions and secondary wound complication and scarring risk is greater. If autologous tissue is harvested from the leg (fascia lata) this is yet another surgical site that can have wound complications, scarring and unwanted cosmesis and nerve problems.

For the Ethicon POP devices, the mesh does not reside in the vagina or in the wall of the vagina. As discussed in the responses to Questions 5 and 8, the studies do not show a significantly increased risk in pain, pain with sex (dyspareunia), change in vaginal diameter, caliber or length, or change in sexual function as compared to POP surgery that does not use mesh. Thus, tissue contraction, to the extent it occurs in POP patients, is no different than that seen with native tissue repair.

Question	10. Please could you provide a timeline outlining your understanding and recognition of risks regarding the use of synthetic polymer mesh in pelvic surgery. This may include: initial recognition of the risk, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients.

See **Attachment 6**.

Question	11. Please can you provide details of your relevant policies and protocols, if any, for ensuring that information relevant to patient safety, and learning from adverse events is disseminated. 12. Please describe the steps you take in your post-marketing vigilance, and any policies you've introduced to recognise and respond to events proactively.

Ethicon investigates and responds individually to each complaint it receives. Ethicon is informed of complaints by clinicians and sometimes the MHRA, as well as those received directly by the

patients themselves or their representatives. Where the complaint is received directly from the patients, Ethicon mediates its response through the patient's clinician to assist in it being better understood.

Only a proportion of the complaints received are reportable to the regulator. In the UK, Ethicon complies with its reporting obligations under the Medical Devices Directive, as expanded upon in the Guidelines on a Medical Devices Vigilance System. The obligations under the MDD have been constant since Ethicon started to market mesh medical devices. Whilst the Guidelines have been amended several times in that period, those amendments have not been material to the substantive reporting requirements.

The MDD requires Ethicon to report "incidents" to the MHRA which are defined as any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the death of a patient or to a serious deterioration in their state of health. The MHRA does not ordinarily require reporting of expected and foreseeable side effects which are clearly identified in the IFU, clinically well known when the device is used and performs as intended, and clinically acceptable in terms of the individual patient benefit.

Any information which Ethicon receives that may trigger a reporting obligation is triaged against the MHRA's reporting criteria to decide whether an incident report should be made. This includes information received directly from patients or medical professionals, and information which is picked up from medical literature.

As explained in response to question 16, the safety and efficacy of the Ethicon urogynecologic mesh devices are kept under constant review. As part of this process adverse events are taken into consideration on a global basis, irrespective of whether a formal reporting obligation to the MHRA is triggered.

Question	13. Please can you supply a summary of adverse event reports, with dates of receipt but fully anonymised, related to use of synthetic mesh in pelvic surgery.

Ethicon reports adverse event reports in accordance with regulatory requirements. As explained in our response to Question 12, the Medical Devices Directive requires Ethicon to report "incidents" to the MHRA which are defined as any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the death of a patient or to a serious deterioration in their state of health.

The MHRA does not ordinarily require reporting of expected and foreseeable side effects which are clearly identified in the IFU, clinically well known when the device is used and performs as intended, and clinically acceptable in terms of the individual patient benefit.

Between 14 November 2005 and 22 August 2018, Ethicon submitted a total of 327 manufacturer incident reports relating to pelvic mesh products to the MHRA. Of these, approximately 81% related to the TVT family of products and the balance related to Prolift, Prosima and Gynemesh

PS. During the same period, TVT accounted for more than 90% of all Ethicon pelvic mesh products sold.

Information on reports prior to 2005 is held on historic systems which could not be accessed by the submission deadline. As explained elsewhere in this submission, all complaint information received forms an important element of the ongoing safety assessments and Clinical Evaluation Reviews of the products.

Question	14. In your view, where within the healthcare system does your corporate responsibility lay for disseminating and responding to adverse event reporting begin and end?

Ethicon complies with its reporting obligations under the Medical Devices Directive, reporting to MHRA the required adverse events it learns about, irrespective of the source.

Question	15. Who has the final say on what should be included on the data sheets and patient information leaflets? If you have exceeded the minimum requirements specified by the regulator please provide details.

The review and approval of marketing materials/detail aides to physicians and professional education to surgeon-physicians as well as patient information brochures is carried out pursuant to Ethicon's copy review process. This process has been employed relevant to the Ethicon urogynecologic mesh devices indicated for the treatment of SUI and POP. Under the Copy review process, claims about Ethicon products, services, or promoted surgical procedures must be reviewed and approved by all of the required reviewers prior to use in any promotional materials.

The copy review process at Ethicon for instructions for use ("IFUs") is controlled by a separate review process.

The materials are submitted for copy review by the Copy Originator and given a specific copy review reference number. The materials are reviewed by a multi-disciplinary team relevant to the specific document/material. The multi-disciplinary copy review team can be composed of employees from Medical/Scientific Affairs, Regulatory Affairs, Legal, as well as R&D, Preclinical, Communications and/or Others. Comments and required changes, if any, are gathered and returned to the Copy Originator for incorporation. Upon incorporation of changes and approval, the final approved document/material is generated and may be disseminated. This process is state of the art and regulatory compliant.

Question	16. Please can you describe the elements of your corporate social responsibility policy which relate to the availability of products, and the risk-benefit analysis for products that you manufacture?

Ethicon is part of the Johnson & Johnson family of companies. At the heart of Johnson & Johnson's business decisions lies its Credo, https://www.jnj.com/credo/, which has guided Johnson & Johnson for 75 years and guides all decision making and policies. (https://www.jnj.com/about-jnj/policies-and-statements). The company, through its workforce of over 130,000 employees, strives to improve the health of humanity.

Teams comprised of employees with expertise in science, product development, surgery and other disciplines evaluate the devices both before and after they are marketed. The monitoring, device assessment and risk-benefit analysis processes are maintained in accordance with current regulatory and industry standards. The processes assess the utility, functionality and safety of the device, with different vehicles including conducting safety assessments that assess potential failure modes and causes, reviewing legacy, preclinical and/or clinical data, and carefully assessing the benefits and risks before launching a product.

At regular intervals after launch, the company reviews adverse events to monitor product performance. This process is complemented by conducting or reviewing company sponsored studies, investigator-initiated studies, and other clinical trials performed by clinical and surgical researchers.

Ethicon procedures also require a periodic overall clinical evaluation of the post-marketing safety, data and performance to assess the benefit-to-risk performance of devices. The device's functionality, complaints received, and risk/benefit analyses are reported in Clinical Evaluation Reports ("CERs").

CERs are performed at intervals depending on the device and are risk based depending on the data pertinent to the device. If issues or trends are found that warrant further investigation, we systematically and robustly perform analyses including quality analyses/boards, corrective action plans and other actions. These Ethicon processes are state of the art and are performed in connection with the company's policy to ensure we produce devices that effectively treat burdensome health conditions while balancing the potential risks and benefits suitable for the relevant application.

Question	17. If applicable, please can you provide a brief summary of litigation and/or settlements relevant to your product(s), both within the UK and worldwide?

For this response, Ethicon refers to its 01 August 2018 10-K filing with the United States Securities and Exchange Commission, which states, in part, as follows:

> Claims for personal injury have been made against Ethicon, Inc. (Ethicon) and Johnson & Johnson arising out of Ethicon's pelvic mesh devices used to treat stress urinary incontinence and pelvic organ prolapse. The Company continues to

receive information with respect to potential costs and additional cases. Cases filed in federal courts in the United States have been organized as a multi- district litigation in the United States District Court for the Southern District of West Virginia. The Company has settled or otherwise resolved a majority of the United States cases and the costs associated with these settlements are reflected in the Company's accruals. In addition, class actions and individual personal injury cases or claims have been commenced in various countries outside of the United States, including claims and cases in the United Kingdom, the Netherlands and Belgium, and class actions in Israel, Australia and Canada, seeking damages for alleged injury resulting from Ethicon's pelvic mesh devices. In Australia, a trial of class action issues has been completed and a decision is expected in 2018. The Company has established accruals with respect to product liability litigation associated with Ethicon's pelvic mesh products.

Question	18. Do you contribute to an administrative (non-litigative) redress scheme anywhere in the world, such as the Nordic pharmaceutical insurance schemes? If so, where, and what are the terms of the contribution? What is your evaluation of the scheme?

We understand this to be a reference to schemes in some jurisdictions that have been set up to provide compensation to eligible individuals who have experienced medical (or in some instances, other) injury without having to establish “fault”. Such schemes exist in the Nordic countries and New Zealand, for example. The latter provides for economic losses, whereas the former provides for non-economic damages as well.

In each of the Nordic countries (except Denmark), the Pharma trade association runs a pharma insurance scheme, which, as a trade-association member, Johnson & Johnson participates in as a condition of its membership. Johnson & Johnson pay annual premiums based on our percentage of the sales of all trade association members in each market. The Swedish, Finnish, and Norwegian trade associations have each set up these schemes in a separate entity, i.e. an insurance company.

There are a variety of differing views on the value of such schemes, which the company notes. The company does not wish to take the opportunity here to express an opinion or evaluation on the benefits or otherwise of such schemes.

Additional Request	Please explain the basis for the evidence you are submitting to the Review, how that evidence was selected, the extent to which any relevant material has been withheld and the reasons why.

We have sought to respond with empirical data where available. Where not available (as an example for information requested from events occurring 20 years ago), we have attempted to respond based on the best recollection of people or resources currently available to us. The evidence submitted to the Review has been selected and provided in an effort to assist the Review in its investigation into the use of synthetic mesh in abdominal and vaginal pelvic mesh procedures. Given the voluminous clinical data on the Ethicon devices as discussed in the attachments and based on the time constraints, we have sought to include historical studies that are pertinent to the issues as well as higher level data and long-term studies. This is not a full literature review capturing all studies on the devices as there are over 100 randomized controlled trials on the TVT and TVT-O devices and over 1,000 studies across all the products. Where any material of a confidential or commercially sensitive nature has been withheld, the reasons have been provided.

Additional Request	Please detail any commercial, financial or legal connection or interest in the pharmaceutical and medical devices industry sector (including subsidiaries) or any other body or organisation of interest to the Review.

The Johnson & Johnson family of companies has significant commercial and financial connections and interest in the pharmaceutical and medical devices industry sector. It was founded in 1886 and ever since, Johnson & Johnson has been pioneering healthcare innovation in fields ranging from medical devices to dental care to cutting-edge cancer treatments. With respect to the specific subject of this inquiry, pelvic mesh, it has researched, developed, marketed and sold pelvic mesh medical devices over the past 20+ years.

Additional Request	You may also want to suggest any potential questions that you would like asked of others who may be giving evidence to the Review.

Given that there are a variety of views on the benefits of urogynecologic mesh expressed by the medical community and professional societies and organizations with expertise in urogynecology (including those pertinent to the use of polypropylene midurethral slings and the use of mesh for sacrocolpopexy as expressed by BSUG, IUGA, ICS and others) we trust that their input is being sought but to the extent that it has not, we would suggest that their input be formally requested as to the utility, desirability, usefulness, durability, safety and efficacy of these procedures and devices.

LIST OF ATTACHMENTS

1 Response to Question 2, 5 and 8 (SUI)

2 Response to Question 2, 5 and 8 (POP)

3 Examples of Marketing Literature

4 Instructions For Use (IFUs)

5 Table of changes to IFUs (To be provided)

6 Response to Question 10

7 2000 TVT Surgeon Monograph

8 2007 Prolift Surgeon Monograph

ATTACHMENT 1

Response to Questions 2(a)-(g), 5 and 8

Ethicon Stress Urinary Incontinence (SUI) Devices

2) Please detail for each such device:

a) Premarket testing undertaken;
b) Any clinical evaluation undertaken;
c) Whether conformity was declared on the basis of equivalence to an existing device, and if so, please detail the existing device;
d) Specify the notified body used for the conformity assessment, and the date the conformity assessment was undertaken;
e) Date of CE marking;
f) Any changes to the design
g) Any changes to the indications (please detail);

If you have exceeded the minimum requirements specified by the regulator please provide details.

2.1 This is a combined response to the topics raised in subparts a-g of Question 2. Ethicon marketed two types of synthetic urogynecologic mesh products—those designed to treat stress urinary incontinence (SUI) and those designed to treat pelvic organ prolapse (POP). The mesh used in all such products is made in whole or in part of knitted Prolene polypropylene fibers. Prolene is a proprietary monofilament polypropylene fiber that has been safely used in almost every type of surgery for half a century to include cardiovascular surgery, transplant surgery, and general surgery. In 1969, the United States FDA approved Prolene sutures as safe and effective for use in the body through the New Drug Application process. The FDA's review of Prolene followed extensive testing and analysis by Ethicon. Millions of people around the world have had Prolene sutures permanently implanted in their bodies for decades.

2.2 The use of various types of surgical mesh in the treatment of POP and SUI dates back to the middle of the last century as pelvic surgeons recognized the shortcomings with non-mesh native tissue repairs.[1] Macroporous polypropylene

[1] MOORE J, ARMSTRONG JT, WILLIS SH. The use of tantalum mesh in cystocele with critical report of ten cases. Am J Obstet Gynecol. 1955 May;69(5):1127-35; WILLIAMS TJ, TELINDE RW. The sling operation for urinary incontinence using mersilene ribbon. Obstet Gynecol. 1962 Feb;19:241-5; LANE FE. Repair of posthysterectomy vaginal-vault prolapse. Obstet Gynecol. 1962 Jul;20:72-7; Morgan JE. A sling operation, using Marlex polypropylene mesh, for treatment of recurrent stress incontinence. Am J Obstet Gynecol. 1970 Feb 1;106(3):369-77; Stanton SL, Brindley GS, Holmes DM. Silastic sling for urethral sphincter incompetence in women. Br J Obstet Gynaecol. 1985 Jul;92(7):747-50; Drutz HP, Cha LS. Massive genital and vaginal vault prolapse treated by abdominal-vaginal sacropexy with use of Marlex mesh: review of the literature. Am J Obstet Gynecol. 1987 Feb;156(2):387-92; Horbach NS, Blanco JS, Ostergard DR, Bent AE, Cornella JL. A

mesh, which has been the preferred option for decades now, has a long history of safe use in the human body, and is supported by more clinical data than alternative mesh materials. In the 1970s, Ethicon's Prolene mesh was first used for hernia repair. This same mesh was selected in the 1990s for the Ethicon TVT device which uses a 1.1 centimeter wide strip of Prolene mesh and has been used in every synthetic midurethral SUI sling manufactured by Ethicon since. No material in pelvic surgical history has demonstrated higher biocompatibility than polypropylene and no polypropylene material has been used in more patients or been subject to more peer-reviewed studies than Prolene. Professional gynecologic and urological societies worldwide have endorsed the biocompatibility of polypropylene and have found full length mid-urethral slings such as the Ethicon TVT and TVT-O devices to be the gold standard treatment option for SUI while the use of macroporous polypropylene has been recognized as the gold standard for apical prolapse.

2.3 SUI is a very prevalent condition among women. Traditional surgical options to treat this disorder carried with them significant morbidity, relatively high failure rates, and a high potential for voiding dysfunction. It was within this context that professor Ulf Ulmsten and Peter Petros developed what came to be TVT—Tension free Vaginal Tape. TVT offered surgeons a new surgical approach that was based on the continence mechanism, less invasive, with a shorter recovery, had a reduced risk of voiding dysfunction and would result in acceptable long-term cure rates. During the development process of TVT that spanned many years and was before Ethicon's involvement, Professor Ulmsten tried a wide variety of different synthetic materials before selecting Prolene mesh to be used in the TVT and placed at the midurethra based on their studies and formulation of the Integral Theory.[2] The pathophysiology of SUI was studied and animal and clinical study of the disease state and device were also conducted before TVT's launch as shown in these publications and others.[3] Prolene mesh proved to have the highest biocompatibility and the best properties for successful tissue integration in this application and in the design of the TVT midurethral sling. Minimally invasive midurethral placement of the Prolene polypropylene mesh/tape with an inside-first approach is a design element that flows through all subsequent devices in the TVT family of products.

suburethral sling procedure with polytetrafluoroethylene for the treatment of genuine stress incontinence in patients with low urethral closure pressure. Obstet Gynecol. 1988 Apr;71(4):648-52.

[2] Petros PE, Ulmsten UI. An integral theory and its method for the diagnosis and management of female urinary incontinence. Scand J Urol Nephrol Suppl. 1993;153:1-93; Petros P. Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond: Ulf Ulmsten Memorial Lecture 2014. Int Urogynecol J. 2015 Apr;26(4):471-6.

[3] Ulmsten U, Ekman G, Giertz G, Malmström A. Different biochemical composition of connective tissue in continent and stress incontinent women. Acta Obstet Gynecol Scand. 1987;66(5):455-7; Ulmsten U, Petros P. Intravaginal slingplasty (IVS): an ambulatory surgical procedure for treatment of female urinary incontinence. Scand J Urol Nephrol. 1995 Mar;29(1):75-82.

2.4 CE Marking as well as the requested conformity information for the Ethicon TVT devices is listed below. All of the TVT midurethral sling devices except TVT Secur remain on the market.

Product	Year	Equivalent Device? (Y/N)	Equivalent Device Name	Date of first CE marking	First Notified Body	Current Notified Body
Gynecare TVT	1997	Y	ProteGen Sling	02-Oct-97 [Medscand as Manufacturer] 02-Aug-00 [Ethicon as Manufacturer] 27-May-02 [Blue] 20-Jun-06 [Laser Cut]	TÜV	BSI
Gynecare TVT with Abdominal Guides	2003	Y	GYNECARE TVT	10-Apr-03 20-Jun-06 [Laser Cut]	TÜV	BSI
Gynecare TVT-O	2003	Y	Gynecare TVT	22-Dec-03	TÜV	BSI
Gynecare TVT-Secur	2006	Y	GYNECARE TVT	8-May-06	BSI	BSI
Gynecare TVT-Abbrevo	2010	Y	GYNECARE TVT Obturator	27-Aug-10	BSI	BSI
Gynecare TVT-Exact	2010	Y	GYNECARE TVT	2-Jun-10	BSI	BSI

2.5 The first published TVT study followed women for two years post-implant.[4] It found that out of the 75 patients implanted with TVT, 92% of the patients were cured or significantly cured of their SUI during that two year period. TVT was first marketed in Europe in 1997. In 2002, Drs. Karen Ward and Paul Hilton (on behalf of the United Kington and Ireland Tension-free Vaginal Tape Trial Group) published the six month

[4] Ulmsten U, Henriksson L, Johnson P, Varhos G. An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1996;7(2):81-5; discussion 85-6.

results of a multicenter randomized trial comparing TVT to the Burch Colposuspension procedure.[5] Ethicon provided the products and additional support to the collaborating centers. This study was a landmark RCT that provided level 1 evidence to the medical community that TVT was set to be the new gold standard based on its benefits of providing patients with a rapid return to normal activities and shorter hospital stays compared to the Burch. Also by the early 2000s, there was 5-year data on the TVT device[6] and the results of other early level 1 randomized controlled trials which showed the safety, benefits and efficacy of the TVT device.[7] By comparison, it took many decades before the first randomized controlled trials were performed after the description of the autologous sling and colposuspension non-mesh surgeries for SUI treatment. Further these data supported the launch of what would become the TVT-O device as discussed below.

2.6 In 2001, the "outside-in" transobturator approach to placing a polypropylene sling to treat SUI was described (outside-in refers to initiating the tape placement through a skin incision and directing it through a periurethral incision, whereas the inside-out transobturator technique which is unique to Ethicon's TVT-O and TVT Abbrevo devices, refers to initiating the placement through the vaginal incision and then outward laterally). The Ethicon TVT-O device was invented by Professor Jean De Leval, in Belgium. He used the same mesh utilized in TVT but surgically implanted it with an "inside-out" midurethral approach through the obturator space as opposed to a retropubic approach like TVT or an outside-in transobturator placement as had been previously described. Prior to TVT-O's launch, Professor De Leval had studied the TVT-O procedure in 138 patients who were enrolled in a study that compared their results to 134 patients implanted with TVT. The results of this study showed similar efficacy to TVT and lower rates of bladder perforations. While it did reveal a 26% rate of thigh pain, this proved to be a transient problem resolving within 24-48 hours of surgery. TVT-O was first marketed in 2004.

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[5] Ward K, et al. Prospective Multicentre Randomised Trial of Tension-Free Vaginal Tape and Colposuspension as Primary Treatment for Stress Incontinence. BMJ, 2002. 325:67.

[6] Nilsson CG, Kuuva N, Falconer C, Rezapour M, Ulmsten U. Long-term results of the tension-free vaginal tape (TVT) procedure for surgical treatment of female stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12 Suppl 2:S5-8

[7] Liapis A, Bakas P, Creatsas G. Burch colposuspension and tension-free vaginal tape in the management of stress urinary incontinence in women. European Urology. 2002;41(4):469–73; Ustun Y, Engin-Ustun Y, Gungor M, Tezcan S. Tension-free vaginal tape compared with laparoscopic Burch urethropexy. Journal of the American Association of Gynecologic Laparoscopists. 2003;10(3):386–9; Valpas A, Kivela A, Penttinen J, Kujansuu E, Haarala M, Nilsson CG. Tension-free vaginal tape and laparoscopic mesh colposuspension for stress urinary incontinence. Obstetrics and Gynecology. 2004;104(1):42–9; Paraiso MF, Walters MD, Karram MM, Barber MD. Laparoscopic Burch colposuspension versus tension-free vaginal tape: a randomized trial. Obstetrics and Gynecology. 2004;104(6):1249–58**;** Ward KL, Hilton P; UK and Ireland TVT Trial Group. A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: two-year follow-up. Am J Obstet Gynecol. 2004 Feb;190(2):324-31.

2.7 In 2006 Ethicon launched the TVT Secur. TVT Secur used the same mesh as TVT and TVT-O and was designed as a single-incision sling. Unlike TVT and TVT-O, it had no exit points and was placed using inserters with fleece tips that enabled fixation of the mesh into the surrounding tissue. At 8 cm in length, TVT Secur was designed to provide the patient with an even less invasive implantation as TVT and TVT-O. TVT Secur was developed with surgeon consultants who developed the procedure which allowed for retropubic or transobturator orientation. TVT Secur's components were studied, refined, and validated in human and animal cadaver studies. Moreover, prior to launching TVT Secur, Ethicon conducted numerous cadaver labs and animal studies to evaluate pullout strength and fixation forces and holding ability of the mesh. A short term trial in patients was also conducted prior to launch. These labs and studies coupled with the decade long clinical history of TVT and TVT-O demonstrated the safety and efficacy of TVT Secur. Following its launch, numerous clinical studies, randomized controlled trials and systematic reviews demonstrated that the safety profile of TVT Secur is similar to that of TVT and TVT-O. In fact, one systematic review compared TVT Secur to retropubic and trans-obturator slings (to include TVT and TVT-O) and found similarly low rates of complications.[8] While some studies have demonstrated a lower efficacy rate for TVT Secur, this has often been attributed to the initial learning curve some surgeons experienced when they first used the product. Indeed, studies that have factored in this learning curve have found similar efficacy rates to TVT and TVT-O once the surgeon's learning curve is overcome. In 2012 Ethicon discontinued the worldwide sale of TVT Secur. This decision was not based on any safety or efficacy concerns but rather the business and medico-legal environment at the time. TVT, TVT-O, TVT Abbrevo, and TVT Exact are still currently marketed products in the UK and worldwide. There has never been a change to the indication for any of these products.

2.8 In 2010 Ethicon launched the TVT Abbrevo device. Like TVT-O, this device was invented by Professor De Leval and placed the same 1.1 cm wide Prolene polypropylene mesh as TVT-O in the same manner through the obturator space using helical passers and a winged guide. Unlike TVT-O, TVT Abbrevo featured a sling that was 12 cm long. In addition to the short and long term data available for TVT and TVT-O prior to the launch of TVT Abbrevo, a study by the Department of Urology at the University of Liege, Belgium demonstrated similar efficacy for TVT Abbrevo when compared to TVT-O. This study was accepted for publication prior to the launch of TVT Abbrevo. The one and three year follow-up results confirmed that TVT Abbrevo is a safe and effective treatment option with complication rates and objective and

[8] Schimpf MO, Rahn DD, Wheeler TL, Patel M, White AB, Orejuela FJ, El-Nashar SA, Margulies RU, Gleason JL, Aschkenazi SO, Mamik MM, Ward RM, Balk EM, Sung VW; Society of Gynecologic Surgeons Systematic Review Group.. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014 Jul;211(1):71.e1-71.e27.

subjective cure rates similar to TVT and TVT-O.[9] Numerous other studies since its launch have come to the same conclusions.

2.9 In 2010 Ethicon launched the TVT Exact device. This device is the second generation of the original TVT and nearly identical to TVT. The mesh, its length and its placement are unchanged from the original TVT. The two devices, by design, provide for the placement of an identical 1.1 cm-wide sling of Prolene polypropylene mesh, using trocars with the same curvature and tip radius. However, the TVT Exact has a narrower trocar (3.0 mm, and 4.2 mm when covered in the smooth plastic, closed-tip trocar sheath) designed to minimize the risk of bladder and tissue damage/perforation, along with a disposable trocar handle. TVT's twelve years of rigorous clinical study of the highest levels of evidence supported Ethicon's determination prior to its launch that TVT Exact was a safe and effective device for treating SUI. Studies have been published demonstrating equivalent efficacy and safety data with the original TVT device and the TVT Exact, suggesting no differences in continence success rates, patient satisfaction, or overall complication rates[10].

2.10 Over the last 20 years there have been two manufacturing changes to the mesh in the TVT devices. Initially the TVT mesh was made using clear Prolene Mesh. In 2001, Ethicon created TVT Blue Prolene mesh, which is identical in construction to the clear Prolene mesh with the exception of the change in pigmentation with the addition of blue striping. This change enhanced the intraoperative visibility of the mesh. In 2006, Ethicon introduced an additional way to cut the mesh for the TVT devices by using a laser instead of the traditional mechanical cutting. TVT and TVT-O are provided in either mechanical or laser cut and TVT Abbrevo and TVT Exact are laser cut.

[9] de Leval J, Thomas A, Waltregny D. The original versus a modified inside-out transobturator procedure: 1-year results of a prospective randomized trial. Int Urogynecol J. 2011 Feb;22(2):145-56; Waltregny D, de Leval J. New surgical technique for treatment of stress urinary incontinence TVT-ABBREVO from development to clinical experience. Surg Technol Int. 2012 Dec;22:149-57.

[10] Thubert T, Canel V, Vinchant M, Wigniolle I, Fernandez H, Deffieux X. Bladder injury and success rates following retropubic mid-urethral sling: TVT EXACT™ vs. TVT™. Eur J Obstet Gynecol Reprod Biol. 2016 Mar;198:78-83.

5) Please share any evidence of positive feedback on pelvic mesh from clinicians or patient groups.

8) Please provide details of any post-marketing vigilance studies of relevance to the Review, including 522 studies if appropriate

RESPONSE:

5,8.1 The following is a combined response to Questions 5 and 8. Over the last 20 years, over 150 randomized controlled trials have examined TVT and approximately 100 have been conducted on TVT-O. These highest-level studies overwhelmingly demonstrate that TVT and TVT-O are safe and effective, offering higher efficacy rates than the traditional native tissue surgeries and low rates of complications. More than 2,000 clinical studies regarding full length polypropylene slings have been performed and support their use.

5,8.2 TVT and TVT-O have also been the subject of a large number of long term studies. These studies have found long term efficacy rates between 80-90% and low rates of complications reported long term. Many of these studies are in excess of 3-5 years, there are numerous studies of 10 years duration or longer with the longest being three separate studies which follow patients for 17 years.[11] (Nilsson 2013, Bakas 2018, Braga 2018). Even at 17 year follow-up TVT demonstrated high objective and subjective cure rates. A systematic review of medium and long term studies of midurethral slings was published in 2015 which included 49 studies and all but one study included an Ethicon TVT family product, documenting that they are by far the most studied and longest studied devices.[12] No other surgery or medical device designed to treat SUI has more supporting long term data.

5,8.3 Meta-analyses and systematic reviews, which are the highest level of evidence available, have also found TVT and TVT-O to be safe and effective with low rates of

[11] Nilsson CG, Palva K, Aarnio R, Morcos E, Falconer C. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265-9. doi: 10.1007/s00192-013-2090-2. Epub 2013 Apr 6; Braga A, Caccia G, Sorice P, Cantaluppi S, Coluccia AC, Di Dedda MC, Regusci L, Ghezzi F, Uccella S, Serati M. Tension-free vaginal tape for treatment of pure urodynamic stress urinary incontinence: efficacy and adverse effects at 17-year follow-up. BJU Int. 2018 Jul;122(1):113-117; Bakas P, Papadakis E, Karachalios C, Liapis I, Panagopoulos N, Liapis A. Assessment of the long-term outcome of TVT procedure for stress urinary incontinence in a female population: results at 17 years' follow-up. Int Urogynecol J. 2018 Jul 7. doi: 10.1007/s00192-018-3713-4. [Epub ahead of print].

[12] Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253-68.

complications.[13] Of note, these reviews have consistently found only a 1-3% mesh exposure rate. As with the long term data the vast bulk of these data are derived from the Ethicon TVT devices. The Cochrane Review by Ogah et al. reported on 62 trials involving 7,101 women and found that minimally invasive suburethral sling operations including TVT and TVT-O "appeared to be as effective as traditional suburethral slings . . . but with shorter operating time and less post-operative voiding dysfunction and de novo urgency symptoms." When comparing mid-urethral sling operations to open retropubic colposuspension procedures like the Burch procedure, they found that mid-urethral sling operations "appeared to be as effective as open retropubic colposuspension . . . with fewer perioperative complications, less postoperative voiding dysfunction, shorter operative time and hospital stay but significantly more bladder perforations . . . ." The authors found that the evidence conflicted on the efficacy of mid-urethral slings in comparison to laparoscopic colposuspension in the short term, but the mid-urethral sling procedures resulted in significantly less de novo urgency and urge incontinence, shorter operating time, hospital stay, and time to return to daily activities. The authors also found that monofilament tapes like the TVT family of products had higher objective cure rates compared to multifilament tapes, and the monofilament tapes also had fewer tape erosions (TVT 1.3% versus 6% for multifilament tapes). They observed that transobturator mid-urethral sling procedures had lower objective cure rates (84% vs. 88%) than retropubic mid-urethral sling procedures, but there was no difference in the rates of subjective cure. The transobturator route was, however, found to involve less voiding dysfunction, less blood loss, less bladder perforation, and shorter operating time. The authors found that the TVT retropubic bottom-to-top route was more effective than top-to-bottom route (used with the AMS SPARC device) and incurred significantly less voiding dysfunction, bladder perforations, and tape erosions.

[13] Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006375; Novara G, Artibani W, Barber MD, Chapple CR, Costantini E, Ficarra V, Hilton P, Nilsson CG, Waltregny D. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol. 2010 Aug;58(2):218-38; Schimpf MO, Rahn DD, Wheeler TL, Patel M, White AB, Orejuela FJ, El-Nashar SA, Margulies RU, Gleason JL, Aschkenazi SO, Mamik MM, Ward RM, Balk EM, Sung VW; Society of Gynecologic Surgeons Systematic Review Group.. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014 Jul;211(1):71.e1-71.e27; Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253-68; Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;(7):CD006375. Update in: Cochrane Database Syst Rev. 2017 Jul 31;7:CD006375; Fusco F, Abdel-Fattah M, Chapple CR, Creta M, La Falce S, Waltregny D, Novara G. Updated Systematic Review and Meta-analysis of the Comparative Data on Colposuspensions, Pubovaginal Slings, and Midurethral Tapes in the Surgical Treatment of Female Stress Urinary Incontinence. Eur Urol. 2017 Oct;72(4):567-591

5,8.4 The more recent Cochrane review by Ford et al. analyzed 55 trials involving 8,652 women and compared the use of the transobturator route (utilized with the TVT-O and TVT-Abbrevo slings) and retropubic route (utilized with the TVT and TVT-Exact slings). The authors observed that an analysis of the 81 trials "showed that over 80% of women with stress urinary incontinence are cured, or have significant improvement in their symptoms, with either [transobturator or retropubic] operation, for up to five years after surgery." The information available on patients' quality of life following the procedures showed "that it improves as a result of these operations, though there is no clear difference between the two procedures." The authors noted that the overall rate of adverse events following mid-urethral sling implantation was low, but retropubic slings had higher morbidity than transobturator slings. Ford and colleagues observed that "[t]he overall rate of vaginal tape erosion/ exposure/ extrusion was low in both [RPR and TOR] groups: 24/1000 instances with TOR compared with 21/1000 for RPR" based on 31 studies involving 4,743 women. The authors found that, for retropubic slings like the TVT and TVT-Exact, a bottom-to-top route—the route most commonly used for implantation of the TVT device—was more effective than a top-to-bottom route, resulting in higher rates of subjective cure, decreased voiding dysfunction, fewer bladder perforations, and fewer vaginal tape erosions. The authors noted: "There is moderate quality evidence that overall reported rates of tape-related complications are low, such as erosion of the tape into the vagina at about 2% for both routes of tape insertion. The reported occurrence of problems with sexual intercourse including pain was low, and leakage of urine during intercourse are improved following insertion of these tapes."

Several registries involving the Ethicon TVT devices were also analyzed in the Cochrane review and the authors found that complication rates were low and similar to rates reported in the multitude of RCTs:

TVT	**TVT-O / TOT:**
• Bladder perforation occurred in 2.7% to 3.9% of cases. • Reoperation rates relating to tape insertion or postoperative voiding dysfunction (POVD) ranged from 1.6% to 2.4%. • Urinary retention rate was 1.6%. • Pelvic haematoma occurred in 0.7% to 1.9% of women. • Infection rate was 0.7%.	• Bladder perforation occurred in 0.4% of cases. • Reoperation rates relating to tape insertion ranged from 0.8% to 2.2%. • Urinary retention rate was 0.5%. • Pelvic haematoma occurred in 0.5% of women. • Infection rate was 0.6%. • Vaginal tape erosion/extrusion rate was 0.4%.

TVT	TVT-O / TOT:
• Vaginal tape erosion/extrusion rate was 1.5%. • Groin pain occurred in 0.4% of women.	• Groin pain occurred in 1.6% of women.

5,8.5 Patients have reported that these devices greatly improve their distressing incontinence symptoms and the studies show that patient satisfaction is high with the vast majority of patients being satisfied with the surgery. For example, in a five year randomized controlled trial that compared TVT to TVT-O, patients reported significant improvement in their quality-of life via validated questionnaires including the Urinary Distress Inventory, the Incontinence Impact Questionnaire, the Urinary Incontinence Severity Score, and a Visual Analog Scale (VAS) [Table 4].[14] For example for the VAS, in which 0 represents no urinary problems and 100 represents unbearable urinary problems, the TVT patients reported that their level of urinary problems fell from 65 before surgery to 11 at five years follow up and the TVT-O patients reported that their level of urinary problems fell from 67 before surgery to 9 at five years follow up. In addition, patient satisfaction was very high. Only 2.2% of TVT patients and 0.8% of TVT-O patients reported that their expectations were not met and only 0.7% of TVT patients and 1.5% of TVT-O patients reported that they would NOT recommend TVT and TVT-O to a friend as shown by Table 3:

[14] Laurikainen E, Valpas A, Aukee P, Kivelä A, Rinne K, Takala T, Nilsson CG. Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence. Eur Urol. 2014 Jun;65(6):1109-14.

Table 3 – Patient satisfaction with the tension-free vaginal tape and the transobturator tension-free vaginal tape operations 5 yr postoperatively

	TVT		TVT-O		
Expectations met:					
Completely	84.6%	115/136	85.6%	113/132	NS
Partly	9.6%	13/136	6.1%	8/132	NS
Not at all	2.2%	3/136	0.8%	1/132	NS
Lost to follow-up	3.7%	5/136	6.8%	9/132	NS
Recommend to a friend:					
Yes	92.6%	126/136	88.6%	117/132	NS
Probably	2.9%	4/136	2.3%	3/132	NS
No	0.7%	1/136	1.5%	2/132	NS
Lost to follow-up	3.7%	5/136	6.8%	9/132	NS

TVT = tension-free vaginal tape; TVT-O = transobturator tension-free vaginal tape.

Similarly, Wai et al. reported that women reported high rates of patient satisfaction in the Trial of Midurethral slings (TOMUS), a multicenter, randomized equivalence trial that compared outcomes of the TVT and transobturator mid-urethral slings (TVT-O and TOT Monarc) in women with symptoms of stress predominant urinary incontinence.[15] The authors reported that:

> Both treatment groups experienced high levels of satisfaction (Table 1), with 85.9% in the retropubic and 90.0% in the transobturator group reporting that they were either “mostly” or “completely” satisfied with respect to urine leakage, with no significant difference between the two routes of surgery (p=0.52). The majority of patients were highly satisfied with respect to other measures on the questionnaire, specifically with urgency to urinate, frequency of urination, capability of physical activity, social activity, ability to engage in sexual activity, and from an emotional standpoint (Table 1) with no significant difference between the two procedures. Additionally, more than 95% of participants in both sling groups indicated that they would still choose to have the surgery or recommend it to a family member or friend if they could go back in time with the knowledge and experience they acquired after the surgery.

[15] Wai CY, Curto TM, Zyczynski HM, Stoddard AM, Burgio KL, Brubaker L, Rickey LM, Menefee SA; Urinary Incontinence Treatment Network.. Patient satisfaction after midurethral sling surgery for stress urinary incontinence. Obstet Gynecol. 2013 May;121(5):1009-16.

Maldonado et al analyzed numerous studies and reported that "In addition to objective efficacy and success, MUSs have an excellent rate of satisfaction in the short and intermediate term after placement."[16]

In the recent 17 year TVT study as further discussed below by Braga et al, 89% of patients reported satisfaction with cure and on the patient-satisfaction scale, which grades the patient's degree of satisfaction regarding continence with a 0 showing that the patient is 'not satisfied' to a 10 which shows that the patient was 'satisfied, the patients reported a median score of 10 at 1, 10, 13 and 17 years.[17] Zyczynski et al reported that treatment with TVT and TVT-O/TOT led to significant improvements in sexual function based on patients' reporting in the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire scores at 24 months ($p < 0.0001$).[18] In addition patients reported that pain with sex (dyspareunia), incontinence during sex, and fear of incontinence during sex all significantly improved after surgery. Preoperative urge incontinence was associated with abstinence after surgery ($p=0.02$) and postoperative urge incontinence negatively impacted sexual function ($p=0.047$).

In a study of 483 patients who underwent TVT with 10+ years follow up, 82.6 % of patients reported that they were "very satisfied" with the surgery.[19] The authors reported objective and subjective cure rates of 89.9 % and 76.1 % and observed that the "subjective cure rate and treatment satisfaction rate found in our non-selected patient cohort 10 years after surgery are also encouraging compared with the 44 % cure rate 14 years after Burch colposuspension." These and other long studies as discussed further show that the Ethicon devices lead to high cure rates and patient satisfaction at short, medium and long term follow up.

5,8.6 The TVT devices are the most studied and longest studied options to treat SUI. Data from clinical studies continues to be published supporting the devices. A recent 17 year TVT study reported that no patient required tape release or resection during the 17 years, and that no significant pelvic organ prolapse, vaginal, bladder or urethral

[16] Maldonado PA, Kogutt BK, Wai CY. Patient satisfaction following midurethral sling surgeries. Curr Opin Obstet Gynecol. 2014 Oct;26(5):404-8.

[17] Braga A, Caccia G, Sorice P, Cantaluppi S, Coluccia AC, Di Dedda MC, Regusci L, Ghezzi F, Uccella S, Serati M. Tension-free vaginal tape for treatment of pure urodynamic stress urinary incontinence: efficacy and adverse effects at 17-year follow-up. BJU Int. 2018 Jul;122(1):113-117;

[18] Zyczynski HM, Rickey L, Dyer KY, Wilson T, Stoddard AM, Gormley EA, Hsu Y, Kusek JW, Brubaker L; Urinary Incontinence Treatment Network.. Sexual activity and function in women more than 2 years after midurethral sling placement. Am J Obstet Gynecol. 2012 Nov;207(5):421.e1-6.

[19] Svenningsen R, Staff AC, Schiøtz HA, Western K, Kulseng-Hanssen S. Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J. 2013 Aug;24(8):1271-8.

erosion, or de novo dyspareunia were recorded in the study population.[20] 91% of patients were objectively cured and 89% were subjectively cured. The authors noted that the data showed no significant deterioration in cure rates over 17 years. Another recent 17 year TVT study reported that there were no cases of dyspareunia, pain at the site of the tape insertion, and partner pain during intercourse and there were no cases requiring tape removal. One patient (1.7%) had a mesh exposure documented at 29 months during 17 years follow up that was treated conservatively.[21] There was an 84% objective cure rate, 79% had subjective cure with another 9% reporting improvement.

A recent updated systematic review and metaanalysis by Fusco et al concluded that the TVT had significantly higher overall and objective cure rates than the Burch colposuspension.[22] TVT and TVT-O had similar rates of objective and subjective efficacy and vaginal mesh exposure (Figure 4F, analysis 01: TVT 1.9% (n=23/1200) versus TVT-O 2.3% (n=27/1157); OR 0.84, CI 0.49 – 1.45, p=0.53). TVT had a significantly lower rate of vaginal mesh exposure than the outside-in TOT. (Figure 4F, analysis 02: TVT 1.6% (n=12/755) versus TOT 4.0% (n=27/667); OR 0.41, CI 0.22 – 0.78, p=0.006). The rate of vaginal mesh exposure with TVT-O was less than outside-in TOT but did not reach statistical significance (Figure 5D: TVT-O 1.7% (n=5/289) versus TOT 4.6% (n=11/237); OR 0.37, CI 0.13 – 1.03, p=0.06). The rate of vaginal perforation with TVT-O was significantly less than outside in TOT (Figure 5C: TVT-O 2.6% (n=7/270) versus TOT 11.8% (n=32/271); OR 0.21, CI 0.09 – 0.47, p=0.0002).

5,8.7 In short, Professor Ulmsten's and Professor De Leval's initial clinical data have been replicated and verified repeatedly over the last 20 years. No other pelvic floor surgery or medical device has been subjected to more scientific scrutiny than TVT and TVT-O. This scrutiny has consistently demonstrated that both products are safe, effective and result in relatively low complication rates. The vast amount of data supporting TVT and TVT-O are reflected in the conclusions of nearly every gynecologic and urologic professional society across the globe as identified and discussed further below. These societies have repeatedly found that full length slings like TVT and TVT-O are safe and effective and a standard of care treatment for SUI.

[20] Braga A, Caccia G, Sorice P, Cantaluppi S, Coluccia AC, Di Dedda MC, Regusci L, Ghezzi F, Uccella S, Serati M. Tension-free vaginal tape for treatment of pure urodynamic stress urinary incontinence: efficacy and adverse effects at 17-year follow-up. BJU Int. 2018 Jul;122(1):113-117;

[21] Bakas P, Papadakis E, Karachalios C, Liapis I, Panagopoulos N, Liapis A. Assessment of the long-term outcome of TVT procedure for stress urinary incontinence in a female population: results at 17 years' follow-up. Int Urogynecol J. 2018 Jul 7. doi: 10.1007/s00192-018-3713-4. [Epub ahead of print].

[22] Fusco F, Abdel-Fattah M, Chapple CR, Creta M, La Falce S, Waltregny D, Novara G. Updated Systematic Review and Meta-analysis of the Comparative Data on Colposuspensions, Pubovaginal Slings, and Midurethral Tapes in the Surgical Treatment of Female Stress Urinary Incontinence. Eur Urol. 2017 Oct;72(4):567-591

For example, in 2018 the American Urogynecologic Society (AUGS) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) reissued a joint position statement that was joined, among others, by the International Urogynecological Association (IUGA). All of these organizations in this statement affirmed their support for mesh devices like TVT and TVT-O finding that they are "safe and effective" and are "probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence." Likewise, the European Association of Urology has also concluded full length polypropylene slings designed to treat SUI are safe and effective treatment options.

5,8.8 In 2013 after conducting its own systematic review of the available medical literature that follow-up on patients up to one year, the FDA also concluded that full length polypropylene slings like TVT and TVT-O are safe and effective devices for the treatment of SUI.

5,8.9 As discussed earlier, gynecologic and urologic professional societies across the globe have repeatedly found that full length slings like TVT and TVT-O are safe and effective and a standard of care treatment for SUI. For example, in 2018 the American Urogynecologic Society (AUGS) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) reissued a joint position statement that was joined, among others, by the International Urogynecological Association (IUGA). All of these organizations in this statement affirmed their support for mesh devices like TVT and TVT-O finding that they are "safe and effective" and are "probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence."

5,8.10 Likewise, in 2017 the European Association of Urology also concluded full length polypropylene slings designed to treat SUI are safe and effective treatment options:

> MUS using synthetic PP tape is the recommended method of surgical approach for the correction of SUI in the 2016 EAU guidelines. Both retropubic and transobturator (TO) approaches are well-established standard MUSs within clinical practice. The 2015 Cochrane review and the recent SCENIHR report concluded that synthetic MUSs are the most extensively researched surgical treatment for SUI, with over 200 published clinical trials establishing its effectiveness and good safety profile.

5,8.11 Professional society statements concluding that full length slings like TVT and TVT-O are safe and effective include:

- American Urological Association 2011 – "AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence" (Board of Directors 2011, https://www.auanet.org/guidelines/use-of-vaginal-mesh-for-the-surgical-treatment-of-stress-urinary-incontinence)

- European Association of Urology 2011 – "EAU Guidelines on Urinary Incontinence" (Thuroff J, et al. European Urology 200; 5 9: 387–400)

- American Urological Association 2012 – "Guideline for the Surgical Management of Female Stress Urinary Incontinence: 2009 Update" (Appell R, et al. https://www.auanet.org/Documents/education/clinical-guidance/Incontinence.pdf)

- Canadian Urological Association 2012 – "Update: Guidelines for Adult Urinary Incontinence Collaborative Consensus Document for the Canadian Urological Association" (Bettez M, et al. Can Urol Assoc J 2012;6(5):354-63)

- European Association of Urology 2012 - "EAU Guidelines on Surgical Treatment of Urinary Incontinence" (Lucas M, et al. Eur Urol 2012; 62: 1118-1129)

- American Urological Association 2013 – "AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence" (https://www.auanet.org/about/vaginal-mesh-for-sui.cfm)

- American Urogynecologic Society and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction 2014 – "Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence" (https://www.augs.org/assets/1/6/AUGS-SUFU_MUS_Position_Statement.pdf)

- International Urogynecological Association 2014 – "Position Statement on Mid-Urethral Slings for Stress Urinary Incontinence" (https://www.iuga.org/files/48/Position-Statements/6/Position-Statement-on-Mid-Urethral-Slings-for-SUI.pdf?preview=1)

- Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and Urogynaecological Society of Australasia (UGSA) 2014 - "Position statement on midurethral slings C-GYN 32"

- American College of Obstetricians and Gynecologist (ACOG) and American Urogynecological Association (AUGS) 2015 – "Practice Bulletin Summary, Clinical Management Guidelines No. 155, Urinary Incontinence in Women"

[replaces 63 from June 2005] (Full located at Obstet Gynecol 2015;126(5):e66-e81, Summary located at at Obstet Gynecol 2015;126(5):1120-1122 and Female Pelvic Med Reconstr Surg 2015;21: 304–314)

- European Association of Urology (EAU) 2015 – "Guidelines on Urinary Incontinence" (Lucas M, et al. http://uroweb.org/wp-content/uploads/20-Urinary-Incontinence_LR1.pdf)

- American Urogynecologic Society and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction 2016 (reaffirmed 2014 version with added participants American College of Obstetricians and Gynecologists, Society of Gynecologic Surgeons, American Association of Gynecologic Laparoscopist, National Association of Female Continence, Womens' Health Foundation) – "Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence" (https://www.augs.org/assets/1/6/AUGS-SUFU_MUS_Position_Statement.pdf)

- European Urology Association (EUA) and European Urogynaecological Association (EUGA) 2017 - "Consensus Statement on the Use of Implanted Materials for Treating Pelvic Organ Prolapse and Stress Urinary Incontinence" (Eur Urol. 2017 Sep; 72(3):424-431)

- International Continence Society, et al. 2017 – "6th International Consultation on Incontinence. Incontinence"

- American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) 2017 – "Surgical Treatment of Female Stress Urinary Incontinence: AUA/SUFU Guideline" (https://www.auanet.org/guidelines/incontinence-stress-urinary-incontinence-(2017)

- Society of Obstetricians and Gynaecologists of Canada 2017 - SOGC Reaffirmed Guidelines. No. 248 Guidelines for the Evaluation and Treatment of Recurrent Urinary Incontinence Following Pelvic Floor Surgery" [Reaffirmed 2015, Replaces No. 74 July 1998] (Lovatsis D, et al. J Obstet Gynaecol Can 2017;39(9):e309ee314)

- Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and Urogynaecological Society of Australasia (UGSA) 2017 - "Position statement on midurethral slings C-GYN 32" (revised from 2014)

- American Urogynecologic Society and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction 2018 (reaffirmed 2014 and 2016 versions with added participants American College of Obstetricians and Gynecologists, Society of Gynecologic Surgeons, American Association of Gynecologic Laparoscopist, National Association of Female Continence, Womens' Health Foundation) – "Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence"

5,8.12 As discussed later, for each of its devices, Ethicon prepared Clinical Evaluation and Expert Reports, which contain postmarketing surveillance data and medical literature analyses, which enables Ethicon to identify risks over time. Ethicon also uses Medical Device Reporting, which is a postmarketing surveillance tool utilized by the FDA, and Medical Device Vigilance Reporting, which is a postmarketing tool utilized by governing regulatory agencies in the European Union. These complaint reports monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of devices. In addition, Ethicon has supported numerous postmarketing clinical studies on its TVT devices as later discussed. All of these postmarketing surveillance activities reflect what the vast body of medical literature and professional societies' statements have concluded—that TVT, TVT-O, TVT Abbrevo and TVT Exact remain safe and effective standard of care treatment options for SUI.

ATTACHMENT 2

Response to Questions 2(a)-(g), 5 and 8

Ethicon Pelvic Organ Prolapse (POP) Mesh Devices

2) Please detail for each such device:

a) Premarket testing undertaken;
b) Any clinical evaluation undertaken;
c) Whether conformity was declared on the basis of equivalence to an existing device, and if so, please detail the existing device;
d) Specify the notified body used for the conformity assessment, and the date the conformity assessment was undertaken;
e) Date of CE marking;
f) Any changes to the design
g) Any changes to the indications (please detail);

If you have exceeded the minimum requirements specified by the regulator please provide details.

2.11 This is a combined response to the topics raised in subparts a-g of Question 2. Pelvic organ prolapse (POP) is a condition in women that occurs when the pelvic organs such as the bladder, uterus, intestines or rectum fall from their normal position. Prolapse occurs because tissue that holds the organs in their proper position are weakened or damaged. As a result, one or more of these organs can bulge into the vagina and in some women protrude outside the vagina. Symptoms include the woman feeling the bulge in the vagina, feeling and seeing the bulge outside the vagina, heaviness or fullness in the vagina, pain in general and with sex, and problems with urination and having a bowel movement. Sexual function can be adversely affected. These prolapse symptoms can be very distressing to women and adversely affect their quality of life.

Pelvic organ prolapse can be surgically treated with “native tissue” (non-mesh) surgery or mesh based surgery. A problem with native tissue prolapse surgery is that it relies heavily on these weakened and damaged tissues that have failed already leading to the prolapse. As a result, native tissue prolapse repairs have higher rates of recurrence (where the condition returns after surgery).

Ethicon’s devices for the surgical treatment of pelvic organ prolapse are also comprised of a Prolene® polypropylene based mesh with some having an absorbable non-Prolene component as discussed below.

Ethicon’s Gynecare Gynemesh® PS Nonabsorbable Prolene Soft Mesh (Gynemesh PS) was the first device indicated for the treatment of pelvic organ prolapse, and is made of Prolene Soft Mesh. Gynemesh PS is produced in different size sheets of mesh which are cut by the surgeon as needed for the specific POP application and patient. Gynemesh PS is made of smaller diameter Prolene fibers than those used in

Prolene mesh and was knitted with a larger pore size given the larger application and pelvic organs needing support. Gynemesh PS could be placed transvaginally or transabdominally until 2012, when the IFU was changed to recommend transabdominal placement only.

Gynemesh PS was the mesh used in other Ethicon POP transvaginal mesh devices such as Gynecare Prolift* Total, Anterior and Posterior Pelvic Floor Repair Systems ("Prolift") and the Gynecare Prosima* Anterior, Posterior and Combined Pelvic Floor Repair Systems ("Prosima"), and is still on the market today. It is currently used for abdominal sacrocolpopexies, a procedure used to restore the position of the pelvic organs by attaching mesh to the top of the vagina. Gynemesh M® is an Ethicon mesh indicated for pelvic organ prolapse and is partly absorbable as it has Monocryl filaments. Gynecare Gynemesh M™ was also used in the Gynecare Prolift +M* Total, Anterior and Posterior Pelvic Floor Repair Systems and Artisyn™ Y-Shaped Mesh ("Artisyn").

2.12 CE Marking as well as the requested conformity information for the Ethicon POP devices is listed below. As discussed above, Gynemesh PS and Artisyn remain on the market for use in transabdominal vaginal vault prolapse repair.

Product	Year	Equivalent Device? (Y/N)	Equivalent Device Name	Date of first CE marking	First Notified Body	Current Notified Body
Gynecare Gynemesh PS	2003	Y	PROLENE Soft Mesh	20-Mar-03	BSI	BSI
Gynecare Prolift	2005	Y	GYNECARE GYNEMESH PS	11-Feb-05	BSI	BSI
Gynecare Prosima	2007	Y	GYNECARE GYNEMESH PS	12-Apr-07	BSI	BSI
Gynecare Prolift +M	2008	Y	GYNECARE GYNEMESH M	2-Dec-08	BSI	BSI
Gynecare Gynemesh M	2010	Y	GYNEMESH PS and PROLIFT	8-Sep-10	BSI	BSI
Artisyn Y-shaped Mesh	2012	Y	GYNECARE GYNEMESH M	18-Jul-12	BSI	BSI

2.13 Prior to the launch of Gynemesh PS, the company relied on the long history of clinical use of Prolene polypropylene and Prolene mesh and its extensive testing. Surgeons in the field desired a macroporous (large pore) mesh that handled well in the pelvic organ prolapse application. After launch, the company conducted an Ethicon sponsored clinical trial of Gynemesh PS used via the transabdominal and transvaginal routes that showed efficacy and safety in the treatment of pelvic organ prolapse.

2.14 A group of French surgeons and physicians known as the TVM Group in 2000 began investigating a consistent and standardized way to place a standardized shaped mesh for the treatment of prolapse, which led to the development of the Prolift device.[1] The surgeons ultimately chose Gynemesh PS as the mesh to use for TVM because of its monofilament, large pore (Amid type 1) polypropylene properties, ease of handling in the operating room, its ability to provide support to the prolapsed organs, and suitability with the body.

In 2004, the one year prospective results from a US study of Gynemesh PS showed that the mesh helped lift the dropped organs back up into their proper place and had a low rate of significant complications.[2] A larger pore Ethicon Vypro* mesh was assessed but not found suitable for the prolapse application. For the anterior Prolift that would be used to treat a bladder prolapse, the arms of the mesh would pass to and through the arcus tendineus fasciae pelvis (ATFP), a support site in the pelvis that had been used for decades in prolapse surgery. For the posterior Prolift, the arms of the mesh would pass to and through the sacrospinous ligaments which had been in use for decades for prolapse surgery with the non-mesh sacrospinous ligament suspension surgery. The company developed special surgical tools that allowed for easier placement of the mesh, less trauma to the tissues, and the ability to adjust the mesh so it could be placed loosely.

2.15 Publications and presentations on the TVM/Prolift occurred before Prolift's launch, including the Gynemesh PS prospective study noted earlier and at the 2004 Joint ICS and IUGA scientific conference in Paris, France. In total over 700 patients had been studied with Gynemesh PS or TVM before the launch of Prolift. Prospective company sponsored TVM studies in the US and France had been conducted and the interim results were analyzed, demonstrating that it provided good support to the organs that had fallen, helped reduce the bothersome prolapse symptoms, and had acceptable safety.

2.16 The Prosima device also used Gynemesh PS mesh and followed the Prolift device. Like Prolift, the Prosima device underwent many years of study by its developer, Australian urogynecologist Dr. Marcus Carey, including the surgical technique, prototype and mesh configuration. However, the Prosima device allowed the mesh to be placed without the need for needle placement through ligaments. Instead it used a vaginal support device and balloon that was inflated after the mesh was placed to provide support for moderate Stage II-III prolapse and keep the mesh

[1] Debodinance P, Berrocal J, Clavé H, Cosson M, Garbin O, Jacquetin B, Rosenthal C, Salet-Lizée D, Villet R. [Changing attitudes on the surgical treatment of urogenital prolapse: birth of the tension-free vaginal mesh]. J Gynecol Obstet Biol Reprod (Paris). 2004 Nov;33(7):577-88.

[2] Lucente V, Hale D, Miller D, Madigan J. Oral Poster 55 A Clinical Assessment of GYNEMESH PS for the Repair of Pelvic Organ Prolapse (POP). J Pelvic Med Surg. J Pelvic Med Surg. 2004; 10(Supp1): S35.

in position as the tissues healed. Studies began in 2004, including a prospective cohort study and an Ethicon sponsored investigator-initiated randomized controlled trial by Dr. Carey and colleagues.[3] Over time, the device and technique were finalized. Prosima was also studied by Ethicon in a company sponsored prospective trial with 12 month results before device launch, which showed that Prosima helped lift the fallen pelvic organs up, improved distressing prolapse symptoms, and significantly improved the patients' quality of life and sexual function.[4] The company also had extensive data on the performance of Gynemesh PS and its use in Prolift before launch. This included a systematic review which showed that more than 30 studies were reported in the literature involving over 4,000 patients and showed 91% effectiveness. The data also demonstrated low rates of serious complications, and complications that were comparable to native tissue prolapse repair, which is the procedure that was often used to treat pelvic organ prolapse prior to the availability of mesh.

2.17 The Prolift +M Pelvic Floor Repair System was developed on the hypothesis that a reduced overall volume of permanent mesh may lead to less complications, specifically pain and mesh exposure, while being as effective as Prolift (as discussed later in Responses 5 and 8). Thus, Prolift +M was similar to Prolift systems, but utilized a different mesh fabric, known as Gynemesh M. This was a new, partially absorbable mesh manufactured with approximately equal parts of PROLENE polypropylene fibres—both blue and undyed—and absorbable Monocryl* fibres.

Once the mesh was implanted and the Monocryl fibres were absorbed, only the PROLENE polypropylene-based fibres remained. Like the Prolift, the Prolift +M device includes both pre-cut mesh and tools to facilitate the implantation of the mesh. At the time Prolift+M was launched in 2009, Ethicon had more than a decade's experience with a macroporous PROLENE Mesh in incontinence surgery (via the TVT and TVT-O devices). There were many years of data available on Gynemesh PS, Prolift and Prosima. Further, Prolift used the same instruments, anatomical locations and had the same indications as Prolift +M. There was preclinical data on the Gynemesh M mesh and a significant amount of clinical data on a very similar technique employed with the Prolift device as discussed above. Finally, Ethicon had conducted a specific study on Prolift+M and had data available to demonstrate safety and effectiveness of this product.

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[3] Carey M, Slack M, Higgs P, Wynn-Williams M, Cornish A. Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG. 2008 Feb;115(3):391-7; Carey M, Higgs P, Goh J, Lim J, Leong A, Krause H, Cornish A. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial. BJOG. 2009 Sep;116(10):1380-6; Reisenauer C, Shiozawa T, Huebner M, Slack M, Carey MP. Anatomic study of prolapse surgery with nonanchored mesh and a vaginal support device. Am J Obstet Gynecol. 2010 Dec;203(6):590.e1-7.

[4] Zyczynski HM, Carey MP, Smith AR, Gauld JM, Robinson D, Sikirica V, Reisenauer C, Slack M; Prosima Study Investigators.. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol. 2010 Dec;203(6):587.e1-8

2.18 Artisyn Y-Shaped Mesh was introduced as a device to surgically treat vaginal vault prolapse via transabdominal (laparotomy or laparoscopic approach) sacrocolposuspension/sacrocolpopexy. It has the same knitting construction and material composition as Gynemesh M mesh.

As a convenience to the pelvic surgeon, the graft comes prepared as a Y-shape. The vertical stripes on the sacral flap and the horizontal stripes on the anterior and posterior flaps help aid in positioning, trimming and suturing the graft. Before the launch of Artisyn, the company had the above noted data relative to Prolene, Prolene mesh, Gynemesh PS, Prolift and Prolift +M, including additional studies that had been conducted through 2012.

5) Please share any evidence of positive feedback on pelvic mesh from clinicians or patient groups.

8) Please provide details of any post-marketing vigilance studies of relevance to the Review, including 522 studies if appropriate

5,8.12 The following is a combined response to Questions 5 and 8. Like the TVT and TVT-O devices, Gynemesh PS and Prolift represent the most studied devices for pelvic organ prolapse treatment. Over 100 clinical studies have been performed on the devices, including numerous Level 1 randomized controlled trials (RCTs), which provide the highest level of scientific data because they are designed to minimize bias and have a lower risk of error.

While the studies and technical data are further discussed below, overall they show that the Ethicon prolapse devices provide better support than non-mesh native tissue prolapse surgery. They are better at reducing or eliminating the bothersome bulging sensation that comes with having a prolapse and have lower rates of reoperation for prolapse recurrence. Many of these studies use questionnaires to record the patients' perception of symptom bother, distress, effect on different bodily functions, their satisfaction and quality of life before and after surgery. Overall the studies also show that the Ethicon prolapse devices helps to alleviate or reduce the bothersome prolapse symptoms. Patient satisfaction is high and there are also improvements in the patients' reported quality of life. These devices have a positive benefit-to-risk profile and are an important treatment option.

Complications are a risk of all prolapse surgery and there are complications that occur with the Ethicon prolapse devices. The types of complications that can occur with non-mesh and mesh based prolapse surgery are similar. For example, pain with sex (dyspareunia) can occur with both surgery types and the studies show that the rates with the Ethicon prolapse devices are not significantly higher than native tissue surgery. Exposure and erosion of the mesh is a unique complication from using mesh for prolapse. However, exposure and erosion of sutures is a risk with native tissue repairs. Data from the studies is further discussed below.

5,8.13 Based on the highest level of evidence as reflected in systematic reviews and meta-analyses, macroporous polypropylene, including the Gynemesh PS and Prolift devices, leads to better efficacy than native tissue repairs. A systematic review published by SGS in 2016 evaluated 66 comparative studies, of which 38 were randomized trials, and showed that in the anterior vaginal compartment, synthetic nonabsorbable mesh consistently showed improved anatomic and bulge symptom

outcomes compared with native tissue repairs based on meta-analyses.[5] Other subjective outcomes, including urinary incontinence or painful sexual intercourse, generally did not differ. They also found that synthetic nonabsorbable mesh used in multiple vaginal compartments improved anatomic outcomes and there was no difference for subjective outcomes including quality of life and urinary and sexual function.

Mesh exposure (where the mesh can be seen through the vaginal tissue) rates, ranged from 1.4–19% at the anterior compartment and 3–36% when mesh was placed in multiple compartments. As discussed later, mesh exposure is a type of wound complication and wound complications such as suture erosion also occur with native tissue prolapse surgery at similar and higher rates.

5,8.14 In another systematic review by Maher et al. performed in connection with the Fifth International Collaboration on Incontinence, it was reported that "In the eight trials evaluating 553 patients who underwent some form of transvaginal mesh surgery in the management of anterior compartment prolapse none of the patients underwent surgical intervention for vaginal pain or dyspareunia (pain with intercourse)."[6] The mesh exposure rate was 10.4% with 6.3% requiring surgical correction. The authors also reported that "Consistent level 1 evidence demonstrates superior subjective and objective outcomes following anterior transvaginal polypropylene mesh as compared to anterior colporrhaphy (grade A)." Anterior colporrhaphy is a non-mesh procedure that uses sutures to attempt to lift the bladder up from its fallen position.

5,8.15 In the most recent Cochrane review by Maher et al.[7] comparing polypropylene transvaginal mesh repair including Gynemesh PS and Prolift to native tissue prolapse repair:

- Recurrent prolapse on examination was less likely after mesh repair than after native tissue repair using only sutures (RR 0.40, 95% CI 0.30 to 0.53, 21 RCTs, n = 2494);

- Awareness of prolapse at one to three years was less likely after mesh repair (RR 0.66, 95% CI 0.54 to 0.81, 12 RCTs, n = 1614);

[5] Schimpf MO, Abed H, Sanses T, White AB, Lowenstein L, Ward RM, Sung VW, Balk EM, Murphy M; Society of Gynecologic Surgeons Systematic Review Group. Graft and Mesh Use in Transvaginal Prolapse Repair: A Systematic Review. Obstet Gynecol. 2016 Jul;128(1):81-91.

[6] Maher C. Anterior vaginal compartment surgery. Int Urogynecol J. 2013 Nov;24(11):1791-802.

[7] Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Marjoribanks J. Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database Syst Rev. 2016 Feb 9;2:CD012079.

- Rates of repeat surgery for prolapse were lower in the mesh group (RR 0.53, 95% CI 0.31 to 0.88, 12 RCTs, n = 1675);

- There was no evidence of a difference between the groups in rates of repeat surgery for continence (RR 1.07, 95% CI 0.62 to 1.83, 9 RCTs, n = 1284);

- 8% of women in the mesh group required repeat surgery for mesh exposure;
- There was no evidence of a difference between the groups in rates of de novo dyspareunia (pain with sex) (RR 0.92, 95% CI 0.58 to 1.47, 11 RCTs, n = 764) or change in sexual function.

5,8.16 While they reported that more women in the mesh group required repeat surgery for prolapse, stress incontinence, or mesh exposure, this analysis was skewed since mesh exposure was tracked for mesh patients, but similar wound complications were not tracked in patients who received native tissue repair. Native tissue prolapse repairs have related wound complications (like suture erosion/exposure, granulation tissue (which can be inflamed and non-healing tissue), etc.) like the mesh exposures seen with Prolift and Gynemesh PS. These native tissue repair wound complications have not been tracked in the literature with the same level of scrutiny as mesh exposures. However, when tracked in the studies, the data shows that this risk with native tissue repair is similar to - or greater than - the risk of wound complications with Gynemesh PS and Prolift.

Several studies have reported wound complications and suture erosion/exposure rates of 9-44% with native tissue prolapse surgery. Suture erosion and wound separation occurred in 31.3% of patients undergoing native tissue posterior prolapse repair with permanent sutures, 9% with absorbable sutures, and 16.1% of women with permanent sutures had additional surgical intervention.[8] In another study of native tissue prolapse surgery, suture-related complications presented at a mean follow up of 19 months in 36% of patients, 74% of the patients had vaginal bleeding, and 70% of patients with symptoms required suture removal.[9] Another study reported suture-related complications presented at a mean follow up of 10.4 months in 45% of patients including a 36% rate of suture exposure and suture removal was common.[10] In an Ethicon Investigator Initiated Study (IIS) which was stopped early due to a mesh exposure rate exceeding 15% per the study protocol and did not reach its planned

[8] Luck AM, Galvin SL, Theofrastous JP. Suture erosion and wound dehiscence with permanent versus absorbable suture in reconstructive posterior vaginal surgery. Am J Obstet Gynecol. 2005 May;192(5):1626-9.

[9] Toglia MR, Fagan MJ. Suture erosion rates and long-term surgical outcomes in patients undergoing sacrospinous ligament suspension with braided polyester suture. Am J Obstet Gynecol. 2008 May;198(5):600.e1-4.

[10] Yazdany T, Yip S, Bhatia NN, Nguyen JN. Suture complications in a teaching institution among patients undergoing uterosacral ligament suspension with permanent braided suture. Int Urogynecol J. 2010 Jul;21(7):813-8.

recruiting numbers and power, the authors later reported that while the rate of mesh exposure with Prolift was 15.6%, the native tissue arm had a 15.1% rate of suture erosion.[11]

5,8.17 In the recent multicenter randomized controlled trial that compared two non-mesh native tissue prolapse surgeries, the uterosacral ligament suspension (ULS) versus the sacrospinous ligament fixation (SSLF), by 5 years suture exposure occurred in 25.8% in the ULS group and 25.7% in the SSLF group and granulation tissue was present in 28.9% in the ULS group and 18.8% of the SSLF group [Table 3].[12] In addition, failures in both arms of the study continued to accrue and at five years the estimated surgical failure rate was 61.5% in the ULS group and 70.3% in the SSLF group [Table 2]. (This is not surprising as pelvic surgeons turned to mesh augmented repairs decades ago because the high failure rates with native tissue repair which involves using of the patient's already-weakened and deficient tissue.[13]) Thus, while much of the focus has been on mesh exposure, when authors apply the same level of scrutiny to tracking native tissue wound complications, it is clear that the risks of wound complications is not avoided by avoiding mesh repairs.

5,8.18 Dyspareunia, pelvic pain and sexual function are also often tracked in these studies and a subject of contention. It should be noted that dyspareunia, pelvic pain and sexual dysfunction are due to numerous causes and are common in women at baseline and in those with pelvic organ prolapse. For example, a study of patients presenting to family practice or gynecology clinics reported that 46% of the patients had dyspareunia, 39% had pelvic pain, 20% had chronic dyspareunia and/or pelvic

[11] Sokol AI, Iglesia CB, Kudish BI, Gutman RE, Shveiky D, Bercik R, Sokol ER. One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Am J Obstet Gynecol. 2012 Jan;206(1):86.e1-9.

[12] Jelovsek JE, Barber MD, Brubaker L, Norton P, Gantz M, Richter HE, Weidner A, Menefee S, Schaffer J, Pugh N, Meikle S; NICHD Pelvic Floor Disorders Network. Effect of Uterosacral Ligament Suspension vs Sacrospinous Ligament Fixation With or Without Perioperative Behavioral Therapy for Pelvic Organ Vaginal Prolapse on Surgical Outcomes and Prolapse Symptoms at 5 Years in the OPTIMAL Randomized Clinical Trial. JAMA. 2018 Apr 17;319(15):1554-1565.

[13] Benson JT, Lucente V, McClellan E. Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: A prospective randomized study with long-term outcome evaluation. Am J Obstet Gynecol. 1996 Dec;175(6):1418-21; discussion 1421-2 (Surgical effectiveness was optimal in only 29% of the vaginal native tissue prolapse repair group leading to reoperation in 33% of the vaginal group by 2.5 years); Whiteside JL, Weber AM, Meyn LA, Walters MD. Risk factors for prolapse recurrence after vaginal repair. Am J Obstet Gynecol. 2004 Nov;191(5):1533-8 (58% of women had recurrent prolapse (>/=stage II); Paraiso MF, Ballard LA, Walters MD, Lee JC, Mitchinson AR. Pelvic support defects and visceral and sexual function in women treated with sacrospinous ligament suspension and pelvic reconstruction. Am J Obstet Gynecol. 1996 Dec;175(6):1423-31 (42.0% of patients had a support defect in at least one compartment with anterior being the most common, 37%, and 48% of women had clinically significant defects at 10 years); Bedford ND, Seman EI, O'Shea RT, Keirse MJ. Long-term outcomes of laparoscopic repair of cystocoele. Aust N Z J Obstet Gynaecol. 2015 Dec;55(6):588-92 (By 5.2 years follow up, 79% of this native tissue prolapse repair group developed prolapse of at least POPQ stage 2 in one or more compartments, 58% became symptomatic again, and overall, 48% underwent further prolapse surgery, including 30% of patients having a further cystocoele repair.)

pain for more than one year duration, and there were high rates of sexual dysfunction [Table 1].[14] In a study of 237 women presenting with pelvic organ prolapse, these conditions were very prevalent at baseline.[15] Pelvic pain was reported in 44% of women. Of those experiencing some degree of pain, 69% reported that the pain interfered with their quality of life and 60% considered their pain to be getting worse. 69% (72/105 women) reported dyspareunia (45 women with penile insertion and 62 women with deep penetration). 57% (60/105 women) reported that dyspareunia had adversely affected their frequency of intercourse. Other factors that adversely affected sexual relations to some degree in sexually active patients included fecal incontinence (15%), urinary incontinence (27%), pelvic organ prolapse (28%), spousal limitations (37%), and pelvic pain (41%). Vaginal atrophy is another common condition in post menopausal women and dyspareunia rates of over 60% have been reported as well as frequent adverse effects on sexual function.[16]

5,8.19 The overall data in the Level 1 systematic reviews and metaanalyses as well as the RCTs specific to Gynemesh PS and Prolift show that these devices do not lead to a significant increased risk of post-operative dyspareunia (pain with intercourse), new onset dyspareunia or pain, an adverse change in sexual function as assessed by validated PISQ scores, or changes in vaginal length or caliber. Many patients see resolution or improvement in baseline pain and dyspareunia and improvement in sexual function.[17]

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[14] Jamieson DJ, Steege JF. The prevalence of dysmenorrhea, dyspareunia, pelvic pain, and irritable bowel syndrome in primary care practices. Obstet Gynecol. 1996 Jan;87(1):55-8.

[15] Ellerkmann RM, et al. Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol. 2001 Dec;185(6):1332-7.

[16] Simon JA, Nappi RE, Kingsberg SA, Maamari R, Brown V. Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) survey: emotional and physical impact of vaginal discomfort on North American postmenopausal women and their partners. Menopause. 2014 Feb;21(2):137-42; Minkin MJ, Maamari R, Reiter S. Postmenopausal vaginal atrophy: evaluation of treatment with local estrogen therapy. Int J Womens Health. 2014 Mar 12;6:281-8; Palma F, Volpe A, Villa P, Cagnacci A; Writing group of AGATA study.. Vaginal atrophy of women in postmenopause. Results from a multicentric observational study: The AGATA study. Maturitas. 2016 Jan;83:40-4.

[17] Dietz V, Maher C. Pelvic organ prolapse and sexual function. Int Urogynecol J. 2013 Nov;24(11):1853-7; Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Marjoribanks J. Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database Syst Rev. 2016 Feb 9;2:CD012079; Schimpf MO, Abed H, Sanses T, White AB, Lowenstein L, Ward RM, Sung VW, Balk EM, Murphy M; Society of Gynecologic Surgeons Systematic Review Group.. Graft and Mesh Use in Transvaginal Prolapse Repair: A Systematic Review. Obstet Gynecol. 2016 Jul;128(1):81-91; Altman D, Väyrynen T, Engh ME, Axelsen S, Falconer C; Nordic Transvaginal Mesh Group. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med. 2011 May 12;364(19):1826-36. Erratum in: N Engl J Med. 2013 Jan 24;368(4):394; Withagen MI, Milani AL, den Boon J, Vervest HA, Vierhout ME. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial. Obstet Gynecol. 2011 Feb;117(2 Pt 1):242-50; Sokol AI, Iglesia CB, Kudish BI, Gutman RE, Shveiky D, Bercik R, Sokol ER. One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Am J Obstet Gynecol. 2012 Jan;206(1):86.e1-9; El-Nazer MA, Gomaa IA, Ismail Madkour WA, Swidan KH, El-Etriby MA. Anterior colporrhaphy versus repair with mesh for anterior vaginal wall prolapse: a comparative clinical study. Arch Gynecol Obstet. 2012 Oct;286(4):965-72; Halaska M, Maxova K, Sottner O, Svabik K, Mlcoch M, Kolarik D,

5,8.20 For example, Dietz and Maher's[18] meta-analyses of prolapse repair and sexual function showed no significant difference in postoperative and de novo (new onset) dyspareunia or change in sexual function for Gynemesh PS and Prolift compared to native tissue repair:

Table 1 Meta-analysis sexual function data from randomised controlled trials (RCT) comparing transvaginal mesh with native tissue repairs

Reference	De novo dyspareunia		Postoperative dyspareunia		Postoperative PISQ score	
	Vaginal mesh	Native tissue	Mesh	Native tissue	Mesh	Native tissue
Altman et al. [15]			8/110	2/101	33.1±6.7	32.2±7.2
					35.1 (1.4)	35.0 (1.4)
Vollebregt et al. [11]	3/20	2/21				
Carey et al. [12]	5/18	5/12	12/30	13/33	Change −6.9	Change −7.8
Sivaslioglu et al. [14]	2/43	0/42				
Nguyen and Burchette [13]	2/22	4/26	2/23	2/23	33±3 34±6	32±4 33±3
Iglesia et al. [21]	1/11	3/14			31/34	32/35
Milani et al. [17]	3/37	3/29	9/53	12/51	35±5.7	31.5±7.2
					34.0±6.7	34.7±5.7
Total	16/151	17/144	31/216	26/207	0.09 (−0.17, 0.36)	
	(10.6 %)	(11.8 %)	(14.4 %)	(12.5 %)	No difference	

The more recent Cochrane and SGS systematic reviews also showed no difference in dyspareunia and change in sexual function for transvaginal macroporous polypropylene mesh as compared to native tissue prolapse surgery. The Cochrane and SGS reviews are the highest level of evidence due to their ability to combine patient results from numerous studies leading to large numbers of patients observed under similar circumstances.

5,8.20 These systematic reviews also show no benefit with the use of biologic grafts. Biologic graft use for prolapse can also lead to pain with intercourse and sexual dysfunction. Another SGS systematic review and metaanalysis reported that dyspareunia was described in 70 studies for an overall rate of 9.1%, which included

Mala I, Krofta L, Halaska MJ. A multicenter, randomized, prospective, controlled study comparing sacrospinous fixation and transvaginal mesh in the treatment of posthysterectomy vaginal vault prolapse. Am J Obstet Gynecol. 2012 Oct;207(4):301.e1-7; Svabik K, Martan A, Masata J, El-Haddad R, Hubka P. Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial. Ultrasound Obstet Gynecol. 2014 Apr;43(4):365-71; Dos Reis Brandão da Silveira S, Haddad JM, de Jármy-Di Bella ZI, Nastri F, Kawabata MG, da Silva Carramão S, Rodrigues CA, Baracat EC, Auge AP. Multicenter, randomized trial comparing native vaginal tissue repair and synthetic mesh repair for genital prolapse surgical treatment. Int Urogynecol J. 2015 Mar;26(3):335-42; Svabik K, Masata J, Hubka P, Martan A. Randomized trial comparing vaginal mesh repair (Prolift Total) versus sacrospinous vaginal colpopexy (SSF) in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion injury – 6 years follow-up. Int Urogynecol J 2016; 27(Supp.1): S59-60.

[18] Dietz V, Maher C. Pelvic organ prolapse and sexual function. Int Urogynecol J. 2013 Nov;24(11):1853-7.

an 8.9% rate for synthetic mesh versus 9.6% for biological grafts.[19] In addition this study showed that biologic grafts had wound complication rates similar to synthetic mesh. 110 studies reported on erosions with an overall rate of 10.3% (synthetic 10.3% versus biological 10.1%) and 16 studies reported on wound granulation for a rate of 7.8% (synthetic 6.8% versus biological 9.1%).

5,8.21 There are several longer-term studies which show that Gynemesh PS, Prolift, Prosima and Prolift +M are effective, durable and safe. These studies also show significant improvements in prolapse symptoms and quality of life and high levels of patient satisfaction.[20] These studies include follow up out to eight years. For example, Luo et al. recently reported on 8-year data from a cohort of 175 patients who underwent surgery with the Prolift and Prosima devices. The objective cure rate (defined as the lowest point of prolapse never reaching the level of the hymen) was 99.4%, the subjective success rate was 91.4%, and there was a 1.1% mesh exposure rate. Patients reported significant improvements in their symptoms, level of distress, and impression on whether their condition improved after surgery. These measures

[19] Abed H, Rahn DD, Lowenstein L, Balk EM, Clemons JL, Rogers RG; Systematic Review Group of the Society of Gynecologic Surgeons. Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials: a systematic review. Int Urogynecol J. 2011 Jul;22(7):789-98.

[20] Huang WC, et al. Outcome of transvaginal pelvic reconstructive surgery with Prolift after a median of 2 years' follow-up. Int Urogynecol J. 2011 Feb;22(2):197-203; Miller D, et al. Prospective clinical assessment of the transvaginal mesh technique for treatment of pelvic organ prolapse-5-year results. Female Pelvic Med Reconstr Surg. 2011 May;17(3):139-43; de Landsheere L, et al. Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up. Am J Obstet Gynecol. 2012 Jan;206(1):83.e1-7; Chen YS, et al. Midterm prospective comparison of vaginal repair with mesh vs Prolift system devices for prolapse. Eur J Obstet Gynecol Reprod Biol. 2012 Oct;164(2):221-6; Benbouzid S, et al. Pelvic organ prolapse transvaginal repair by the Prolift system: evaluation of efficacy and complications after a 4.5 years follow up. Int J Urol. 2012 Nov;19(11):1010-6; Wang FM, et al. Prospective study of transobturator mesh kit (Prolift™) in pelvic reconstructive surgery with vaginal hysterectomy after 3 years' follow-up. Arch Gynecol Obstet. 2013 Aug;288(2):355-9; Jacquetin B, et al. Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogynecol J. 2013 Oct;24(10):1679-86; Khan ZA, et al. Outcomes and complications of trans-vaginal mesh repair using the Prolift™ kit for pelvic organ prolapse at 4 years median follow-up in a tertiary referral centre. Arch Gynecol Obstet. 2014 Dec;290(6):1151-7; Svabik K, et al. Randomized trial comparing vaginal mesh repair (Prolift Total) versus sacrospinous vaginal colpopexy (SSF) in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion injury – 6 years follow-up. Int Urogynecol J 2016; 27(Supp.1): S59-60; Meyer I, et al. Synthetic Graft Augmentation in Vaginal Prolapse Surgery: Long-Term Objective and Subjective Outcomes. J Minim Invasive Gynecol. 2016 May-Jun;23(4):614-21; Song W, et al. Anatomical and Functional Outcomes of Prolift Transvaginal Mesh for Treatment of Pelvic Organ Prolapse. Low Urin Tract Symptoms. 2016 Sep;8(3):159-64; Santos F, et al. Transvaginal repair of genital prolapse with Prolift™ system: complications and outcomes after 6 years of use – a single-center study. Eur J Obstet Gynecol Reprod Biol. 2016; 206: e102; Lo TS, et al. A 52-month follow-up on the transvaginal mesh surgery in vaginal cuff eversion. Taiwan J Obstet Gynecol. 2017 Jun;56(3):346-352; Kraus P, et al. The results of five years follow-up prospective study of vaginal prolapse repaired by prolift total mesh surgery or sacrospinous fixation. Ceska Gynekol. 2017 Fall;82(4):277-286; Ubertazzi EP, et al. Long-term outcomes of transvaginal mesh (TVM) In patients with pelvic organ prolapse: A 5-year follow-up. Eur J Obstet Gynecol Reprod Biol. 2018 Apr 14;225:90-94; Luo DY, et al. Long term (8-year) Follow-up of Transvaginal Anatomical Implant of Mesh in Pelvic organ prolapse. Sci Rep. 2018 Feb 12;8(1):2829.

were recorded by using standardized questionnaires (the Pelvic Floor Distress Inventory (PFDI-20) and the Patient Global Impression of Improvement (PGI-I) questionnaires). The authors concluded that "the transvaginal anatomical implant technique is effective and safe" and "TVM procedures are feasible with favourable prospects for POP." The 7 year study by Meyer et al. reported that the prolapsed organs were effectively put back in their normal (anatomic) location. The POP-Q system was used, which is a way to measure different anatomic points in the vagina relative to the prolapse. These POP-Q measurements of the anterior, posterior, apical, and overall pelvic organ prolapse stage were significantly improved compared with baseline (all p=0.001) [Table 2]. Only 3 patients (6%) after this long follow up had the leading edge of their prolapse beyond the hymen, which is the point where symptoms frequently present. This shows that the vast majority of patients' organs were lifted up toward the proper location. Subjective cure, which is the patient reporting whether the symptom was cured, was seen in 80% of patients who reported the absence of bulge symptoms. The rate of mesh exposure was 6%. The authors reported that "Women who underwent transvaginal pelvic organ prolapse surgery using the Prolift mesh system continue to demonstrate positive outcomes in terms of restored anatomy, improved symptom specific distress, and enhanced quality of life at 5 years after surgery." It was also observed that "Synthetic graft augmentation in transvaginal pelvic organ prolapse surgery can be a viable option, with positive outcomes at long-term follow-up."

A 7-year Prolift study by Heinonen found a similar 80% patient satisfaction rate and an anatomic success rate of 56-69% depending on the definition. The leading edge of the prolapse was at or above the hymen in 90.7% of patients showing that 9 out of 10 patients had their prolapse reduced to a point where it is less likely to cause bothersome symptoms. There was a 23% rate of mesh exposure with most being asymptomatic and of late onset. The authors explained that the study included the learning curves of several surgeons and "It is possible that, in the beginning, meshes were not implanted deeply enough under the fibromuscular layer, which may have led to insufficient tissue thickness for mesh coverage. Nieminen et al. reported a mesh exposure rate comparable with ours when the mesh was placed subepithelially [5]. Our preliminary results from a subanalysis of this data comparing the complications in the first 100 and the following 95 patients revealed a reduction of exposures from 14% to 5% in the short term."

A 6.5 year RCT comparing Prolift to sacrospinous ligament fixation (SSLF), a non-mesh native tissue prolapse surgery, by Svabik et al. reported that anatomic failure with Prolift was significantly less than SSLF (21% versus 77%, p<0.001). Failure by ultrasound was also significantly less for Prolift (3% versus 58%, p<0.001). 5 patients in the SSLF group underwent reoperation (p=0.016) and patients after SSLF reported that they were significantly less satisfied than the Prolift patients (VAS score p=0.001). There were three mesh exposures (8.3%) with no new mesh exposures occurring between 1 and 6 years. Ubertazzi et al. reported a 79% cure rate in a five-year Prolift

study. 5.5% of patients were re-operated for prolapse recurrence. There was a 16.6% rate of mesh exposure. These results were noted to be comparable to the 5 year TVM studies by Jacquetin et al. and Miller et al., which were Ethicon company sponsored studies. The authors noted that "We found TVM very useful option for POP treatment with long term success and high patient satisfaction, with acceptable rate of complications. We believe that the long-term results might seem encouraging."

A 4.5 year Prolift study by Benbouzid et al. reported a 85% anatomical cure rate, with no patient needing a repeat surgery for recurrence of prolapse, and a 5.3% mesh exposure rate. The authors noted that their mesh exposure rate was comparable to the 38 month Prolift study in 524 patients by de Landsheere et al. It was reported, "In conclusion, Prolift transvaginal mesh system has been shown to be a safe and efficacious technique for POP repair by transvaginal approach with a success rate of 85.3% after a mean follow up of 4.5 years. These results give preliminary data to inspire further comparative studies and should be compared with other long-term reports."

In a 4-year Prolift study by Khan et al., there was a 10% failure rate. New onset prolapse in the non-operated compartment occurred in 19.5%. Mesh exposure was noted in 6 (5.6 %) women throughout the entire study period. A 40-month study by Song et al. reported that optimal or satisfactory anatomic outcomes for anterior, apical, and posterior prolapse occurred in 76.7, 85.0, and 82.5% of cases, respectively. The overall patient satisfaction rate was 84.7%. Five patients (3.1%) were diagnosed with vaginal erosion and treated with partial excision of the mesh without evidence of infection. There was significant improvement in the mean anatomic POP-Q points. Patients also reported significant improvement in distress and symptoms after having surgery with Prolift per their responses to different questionnaires (Mean values for urinary distress inventory (UDI), and pelvic organ prolapsed distress inventory (POPDI) in the Pelvic Floor Distress Inventory (PFDI)). High rates were reported for patients' perception of surgical benefit, satisfaction, willingness to undergo retreatment, and willingness to recommend this treatment to others were 87.7, 89.8, 92.6, and 91.4%, respectively. The authors noted that "Pelvic organ prolapse repair using the Prolift Transvaginal Mesh is an effective and safe procedure without significant complications." The three year results of the Prolift +M company sponsored study reported by Milani et al. showed a 75.9% anatomic cure rate with the leading edge above the hymen in 88% of patients in the treated compartment. The rate of mesh exposure was 14.8%. An 18-month Prolift +M study by Quenemer et al. compared their data to Prolift data by the authors and reported that the rates of reoperation for mesh exposure, mesh complications, recurrence, and urinary complications were low and statistically similar to Prolift. The 29-month results of the company sponsored Prosima study by Sayer et al. reported 69.1% anatomic cure rate with the leading edge above the hymen in 84.5% of patients. Pelvic symptoms and quality of life significantly improved. At ≥2 years, 82.6% of the women reported that

their prolapse was “much better” and another 7.3% reported that their prolapse was “a little better”. The mesh exposure rate was 9.1%.

5,8.22 Gynemesh PS and Artisyn are both employed via sacrocolpopexy, and abdominal surgical procedure used to restore the position of the pelvic organs by attaching mesh to the top of the vagina. In 1962, Lane first described the use of a graft in the repair of vaginal vault prolapse via abdominal sacrocolpopexy (ASC).[21]

5,8.23 Sacrocolpopexy has long been performed with mesh most commonly polypropylene including Prolene polypropylene which has a low rate of mesh exposure.[22] A 2012 survey of members of the American Urogynecologic Society (AUGS) and the International Urogynecology Association (IUGA) reported that when sacrocolpopexy was performed, 99.4 % reported using a polypropylene mesh versus 1 respondent who used cadaveric fascia.[23]

5,8.24 In 1996 Benson et al. reported in a Level 1 RCT that ASC with mesh led to higher efficacy and a lower reoperation rate in a cohort of 80 women randomized to ASC or bilateral SSL fixation and followed up at 2.5 years.[24] Surgical effectiveness was optimal in only 29% of the vaginal native tissue group and 58% of the ASC group and was unsatisfactory leading to reoperation in 33% of the vaginal group and 16% of the ASC group. Reoperations were most common for recurrent cystocele, 12 from the vaginal group (29%) and 4 from the ASC group (10.5%).

5,8.24 Systematic reviews of the highest level surgical literature have established sacrocolpopexy as the gold standard surgical treatment for apical pelvic organ prolapse, yielding the best objective anatomic outcomes, subjective symptom relief, and postsurgical sexual function. [25] The CARE study, which randomized 322 women

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[21] Lane FE. Repair of posthysterectomy vaginal-vault prolapse. Obstet Gynecol. 1962 Jul;20:72-7.

[22] Baker KR, Beresford JM, Campbell C. Colposacropexy with Prolene mesh. Surg Gynecol Obstet. 1990 Jul;171(1):51-4; Iglesia CB, Fenner DE, Brubaker L. The use of mesh in gynecologic surgery. Int Urogynecol J Pelvic Floor Dysfunct. 1997;8(2):105-15; Schettini M, Fortunato P, Gallucci M. Abdominal sacral colpopexy with prolene mesh. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10(5):295-9; Nygaard IE, McCreery R, Brubaker L, Connolly A, Cundiff G, Weber AM, Zyczynski H; Pelvic Floor Disorders Network.. Abdominal sacrocolpopexy: a comprehensive review. Obstet Gynecol. 2004 Oct;104(4):805-23.

[23] O'Sullivan OE, Matthews CA, O'Reilly BA. Sacrocolpopexy: is there a consistent surgical technique? Int Urogynecol J. 2016 May;27(5):747-50.

[24] Benson JT, Lucente V, McClellan E. Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: a prospective randomized study with long-term outcome evaluation. Am J Obstet Gynecol. 1996 Dec;175(6):1418-21.

[25] Nygaard IE, McCreery R, Brubaker L, Connolly A, Cundiff G, Weber AM, Zyczynski H; Pelvic Floor Disorders Network.. Abdominal sacrocolpopexy: a comprehensive review. Obstet Gynecol. 2004 Oct;104(4):805-23; Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD004014. doi: 10.1002/14651858.CD004014.pub5. Review. Update in: Cochrane Database Syst Rev. 2016 Nov 30;11:CD004014.

to abdominal sacrocolpopexy with or without Burch reported a lower rate of mesh complications in the polypropylene group (5.1%).[26] Sacrocolpopexy with Gynemesh and Prolene mesh has been shown to be safe and effective with significant improvement in prolapse symptoms and a low rate of mesh exposure.[27]

5,8.25 The 2013 Cochrane Review conforms the efficacy, safety and durability of sacrocolpopexy with polypropylene mesh for the treatment of pelvic organ prolapse.[28] Sacrocolpopexy was associated with a lower rate of recurrent vaginal vault prolapse and painful intercourse compared to sacrospinous ligament suspension and a higher success rate and lower reoperation rate than vaginal uterosacral ligament suspension. The authors concluded that sacrocolpopexy with polypropylene mesh has superior outcomes and resulted in lower levels of dyspareunia than vaginal apical suspension without mesh. The updated 2016 Cochrane Review included 30 RCTs in 3,414 women comparing surgical procedures for apical vaginal prolapse and found that sacrocolpopexy was associated with a lower risk of awareness of prolapse, recurrent prolapse on examination, repeat surgery for prolapse, postoperative SUI and dyspareunia than a variety of vaginal interventions.[29]

[26] Cundiff GW, Varner E, Visco AG, Zyczynski HM, Nager CW, Norton PA, Schaffer J, Brown MB, Brubaker L; Pelvic Floor Disorders Network. Risk factors for mesh/suture erosion following sacral colpopexy. Am J Obstet Gynecol. 2008 Dec;199(6):688.e1-5.

[27] Agarwala N, Hasiak N, Shade M. Laparoscopic sacral colpopexy with Gynemesh as graft material--experience and results. J Minim Invasive Gynecol. 2007 Sep-Oct;14(5):577-83; Stepanian AA, Miklos JR, Moore RD, Mattox TF. Risk of mesh extrusion and other mesh-related complications after laparoscopic sacral colpopexy with or without concurrent laparoscopic-assisted vaginal hysterectomy: experience of 402 patients. J Minim Invasive Gynecol. 2008 Mar-Apr;15(2):188-96; Loffeld CJ, Thijs S, Mol BW, Bongers MY, Roovers JP. Laparoscopic sacrocolpopexy: a comparison of Prolene and Tutoplast mesh. Acta Obstet Gynecol Scand. 2009;88(7):826-30; Sarlos D, Kots L, Ryu G, Schaer G. Long-term follow-up of laparoscopic sacrocolpopexy. Int Urogynecol J. 2014 Sep;25(9):1207-12.

[28] Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD004014.

[29] Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Brown J. Surgery for women with apical vaginal prolapse. Cochrane Database Syst Rev. 2016 Oct 1;10:CD012376.

ATTACHMENT 3

Examples of Marketing Literature

(Provided via a secure share file site, due to file sizes)

ATTACHMENT 4

Instructions For Use (IFUs)

(Provided via a secure share file site, due to file sizes)

ATTACHMENT 5

Table of changes to IFUs

(Per response this is to be provided at a later time)

ATTACHMENT 6

Response to Question 10

10) Please could you provide a timeline outlining your understanding and recognition of risks regarding the use of synthetic polymer mesh in pelvic surgery.

This may include: initial recognition of the risk, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients.

10.1 Ethicon has been aware of the pertinent risks with the use of its urogynecological synthetic mesh-based devices when they were launched and marketed. This was based on:

- The basic education, training, and experience of the pelvic surgeon relative to gynecologic, vaginal, pelvic, POP and SUI surgery, grafts/meshes, and the implantation of foreign bodies,
- The long use of synthetic mesh in the surgical treatment of POP and SUI before the subject Ethicon urogynecological devices, and
- The long history of medical literature relative to the surgical treatment of POP and SUI and its risks, whether grafts or synthetic mesh are employed.

10.2 During the education and training of pelvic surgeons, which can take over eight years, not only are they trained to do surgery, they are also made aware of the potential risks of gynecologic, vaginal and pelvic surgery, including POP and SUI surgery involving mesh and non-mesh repairs. They are taught and gain experience in anatomy, physiology, disease states, surgical risks, wound healing and complications, the use of foreign materials in surgery, the foreign body response, and many other pertinent areas in the practice of medicine, surgery and female pelvic surgery in particular.

10.3 The risks of POP and SUI surgery are common whether synthetic mesh, a graft, or non-mesh native tissue repairs take place. As discussed earlier, while there is a risk of mesh exposure/erosion with the use of synthetic mesh, there are comparable wound complications in non-mesh surgeries. This includes exposure and erosion of biologic grafts used in POP and SUI surgery, and exposure and erosion of sutures when non-mesh native tissue POP and SUI repairs are performed. Scarring and tissue contraction, as well as pain, dyspareunia (pain with sex), and pelvic pain, are risks of all vaginal, POP and SUI surgeries regardless of whether mesh is used.

10.4 The medical literature on gynecologic, POP and SUI surgery, whether native tissue, grafts or synthetic mesh are used, extensively described the risks to pelvic surgeons well before these devices were on the market. For example, over 100 years ago Lowson in the British Medical Journal reported on voiding problems, dyspareunia

and sexual dysfunction, and other symptoms related to pelvic organ prolapse. Lowson warned that following anterior repair (a non-mesh native tissue prolapse surgery), patients could have pain, recurrence, voiding dysfunction / frequency, and chronic urinary tract infections.[1] In Dr. Fothergill's 1912 lecture on prolapse and prolapse surgery recorded in the British Medical Journal, he warned about healing issues. This included wound complications with different suture materials including potential difficulty in their removal and pain to the patient, infection, shortening of the vaginal wall and narrowing of the vagina, recurrence, and the need for reoperation.[2] He also discussed that the incision size and type, surgical technique, difficulty in vaginal operations, and judgment as well as experience could affect surgical outcomes and complications. In 1920 Swayne described a procedure for the cure of anterior native tissue prolapse surgery and reported that postoperatively there was a "shelf" (scar tissue) across the anterior pelvis produced by tension put on the tissue.[3]

10.5 In one of the first reports of transvaginal graft usage to treat prolapse in 1955, the authors used tantalum mesh due to the high recurrence rates that were well known and reported with native tissue repair. They warned that vaginal discharge, granulation tissue, palpable mesh (mesh that could be felt on exam), mesh exposure and the need to perform mesh excision surgery could occur with the implant, as well as other complications including voiding dysfunction/urgency and frequency, cystitis (UTI), and post-operative incisional infection.[4] The authors also reported that there were risks of fistula, mesh erosion into an organ such as the bladder or urethra, and stress urinary incontinence following surgery, but none were seen in these mesh patients. Similarly, in the first description of the use of mesh to treat prolapse abdominally via sacrocolpopexy in 1962, the author noted that recurrence, impairment of vaginal function, pain, vaginal shortening, and rectal displacement were well reported risks with vaginal prolapse repair.[5]

10.6 Moreover, the risks of dyspareunia (pain with intercourse), pain, scarring, vaginal stenosis, vaginal shortening, tissue contraction, and the need to re-operate with all vaginal, POP, and SUI surgeries were also well known and reported in the 1960s to pelvic surgeons. In the 1961 Journal of Obstetrics and Gynaecology of the British Commonwealth, Francis and Jeffcoate reported in their frequently referenced

[1] Lowson D. An Operation for Elevation of the Female Bladder in Prolapse or Cystocele. Br Med J. 1898 Jul 23;2(1960):232-4.

[2] Fothergill WE. A Clinical Lecture ON THE PRECISE RELATIONSHIP OF CYSTOCELE, PROLAPSE AND RECTOCELE, AND THE OPERATIONS FOR THEIR RELIEF: Delivered in the Post-graduate Course at the Manchester Royal Infirmary. Br Med J. 1912 Apr 13;1(2676):817-8.

[3] Swayne WC. An Operation for the Cure of Prolapse and Cystocele. Bristol Med Chir J (1883). 1920 Jun;37(139):81-87.

[4] Moore J, et al. The use of tantalum mesh in cystocele with critical report of ten cases. Am J Obstet Gynecol. 1955 May;69(5):1127-35.

[5] Lane FE. Repair of posthysterectomy vaginal-vault prolapse. Obstet Gynecol. 1962 Jul;20:72-7.

article "Dyspareunia following vaginal operations" that "Apareunia and dyspareunia are well accepted complications of operations which involve incision and suture of the vagina, and are variously explained. Some authorities emphasize the part played by tenderness of scars in the vaginal walls, others consider that shortening of the vagina, especially following vaginal hysterectomy, is an important factor. But the most obvious cause for post-operative dyspareunia is narrowing of the introitus and the vagina which results from removal of tissue as part of the cure of prolapse."[6]

10.7 These and other risks were also reported in several studies regarding the use of slings to treat SUI in the 1960s, 1970s and 1980s.[7] For example, in 1962 Williams and TeLinde reported on the use of Mersilene in the treatment of SUI in an attempt to forego the harvesting of native tissue (fascia) for SUI surgery, and discussed numerous risks of sling surgery including injury to the bladder and urethra, retention, voiding dysfunction, dysuria, UTI, frequency, urgency, urge incontinence, infection, abscess formation, urethral erosion, granulation tissue, mesh exposure, sinus formation, mesh excision/removal, and recurrence.

10.8 In 1970, Morgan described the use of a polypropylene sling (Marlex) to treat SUI.[8] He discussed risks of autologous and synthetic slings and warned of risks including urethral and bladder laceration, fistula, excessive sling tension leading to obstruction and urethral transection, urethral narrowing, scar formation, infection, urgency, voiding dysfunction, UTI, and recurrence.

10.9 In 1985, Dr. Start Stanton, a well-known British surgeon and urogynecologist, wrote a review article in the British Journal of Obstetrics and Gynaecology about SUI surgery including its risks.[9] In Table 1, he identified some of the complications that could occur including exposure and erosion of the sling:

[6] Francis WJ, Jeffcoate TN. Dyspareunia following vaginal operations. J Obstet Gynaecol Br Commonw. 1961 Feb;68:1-10.

[7] Williams TJ, TeLinde RW. The sling operation for urinary incontinence using mersilene ribbon. Obstet Gynecol. 1962 Feb;19:241-5; Moir JC. The gauze-hammock operation. (A modified Aldridge sling procedure). J Obstet Gynaecol Br Commonw. 1968 Jan;75(1):1-9; Spencer TS, Jequier AM, Kersey HJ. The gauze-hammock operation in the treatment of persistent stress incontinence. J Obstet Gynaecol Br Commonw. 1972 Jul;79(7):666-9; Nichols DH. The Mersilene mesh gauze-hammock for severe urinary stress incontinence. Obstet Gynecol. 1973 Jan;41(1):88-93; Fianu S, Söderberg G. Absorbable polyglactin mesh for retropubic sling operations in female urinary stress incontinence. Gynecol Obstet Invest. 1983;16(1):45-50; Kersey J. The gauze hammock sling operation in the treatment of stress incontinence. Br J Obstet Gynaecol. 1983 Oct;90(10):945-9;

[8] Morgan JE. A sling operation, using Marlex polypropylene mesh, for treatment of recurrent stress incontinence. Am J Obstet Gynecol. 1970 Feb 1;106(3):369-77.

[9] Stanton SL. Stress incontinence: why and how operations work. Clin Obstet Gynaecol. 1985 Jun;12(2):369-77.

Table 1. Complications associated with continence surgery.

Operation	Operative	Postoperative
Anterior repair	Injury to bladder and urethra Venous haemorrhage	Vaginal narrowing Recurrence of incontinence Recurrence of prolapse
Marshall–Machetti–Krantz	Injury to bladder Venous haemorrhage Difficulty in retaining symphyseal sutures Ureteric injury	Osteitis pubis Recurrence of incontinence Voiding difficulty
Colposuspension	Venous haemorrhage Bladder injury Ureteric injury Tearing of lateral vaginal fornix	Voiding difficulty Detrusor instability Recurrence of incontinence Dyspareunia
Sling	Injury to bladder Injury to ureter Venous haemorrhage	Voiding difficulty Exposure/erosion of sling Detrusor instability

Stanton discussed these and other complications of SUI surgery extensively and reported that "If an inorganic sling is used, erosion through the anterior vaginal wall or erosion into the urethra or bladder are known complications. The former may be treated conservatively and observed, with antibiotics prescribed where appropriate. The latter, especially if causing symptoms, needs removal of the sling and closure of any fistula."

Also that year, Stanton reported on the use of a Silastic sling for stress urinary incontinence.[10] This was later followed up by Chin and Stanton on a larger cohort of 88 Silastic sling procedures and it was reported that 22 women developed new onset detrusor instability (an unstable bladder that contracts involuntarily and for no apparent reason leading to sudden or frequent need to urinate) and four patients required removal of the sling for voiding difficulties.[11] 10 patients developed sling erosions including five vaginal erosions, four bladder erosions and one urethral erosion, and after removal of the sling, seven women remained continent.

10.10 Similarly, in 1988, Horbach et al reported on the use of mesh as a sling to treat SUI. They reported on outcomes, complications and reoperation and warned that failure, reoperation, wound complications / erosion / seroma, graft and foreign body

[10] Stanton SL, Brindley GS, Holmes DM. Silastic sling for urethral sphincter incompetence in women. Br J Obstet Gynaecol. 1985 Jul;92(7):747-50.

[11] Chin YK, Stanton SL. A follow up of silastic sling for genuine stress incontinence. Br J Obstet Gynaecol. 1995 Feb;102(2):143-7.

infection and rejection, sinus tract formation, voiding dysfunction and retention and suprapubic catheter usage, urinary urgency and frequency, persistent detrusor instability, surgical exploration, sling division/revision and removal, urethral irritation/erosion/necrosis, and urinary tract infections including recurrent UTI could occur.[12]

10.11 In 1997, a review titled "The Use of Mesh in Gynecologic Surgery" cited to 76 studies and papers as set forth below, and warned of well reported and known risks to pelvic surgeons. This included mesh exposure/erosion, pain, dyspareunia, voiding difficulties, retention, UTIs and urgency, scarring, infection and rejection, bleeding, injury to organs, vessels and nerves, recurrence, and the need to reoperate for these complications.[13] These are basic and well known risks to vaginal and pelvic surgery, and are part of the basic knowledge expected of the pelvic surgeon in light of their education, training, professional experience, certification, and the medical literature.

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10.12 In the 1999 paper by Chaliha and Stanton concerning complications from SUI surgery that was published in the British Journal of Obstetrics and Gynaecology, the authors cited to 98 other papers concerning SUI surgery and its risks. These risks included voiding dysfunction, retention, detrusor instability, wound complications, wound infection, fistula, dyspareunia, chronic pain, mesh exposure, erosion and removal, recurrence, and reoperation.[14] Numerous other publications have been published long ago that discuss the risks of POP and SUI surgery.[15]

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10.13 Also, Ethicon has employed Medical Affairs physicians who are knowledgeable regarding the risks of general surgery and gynecologic, vaginal and pelvic surgery, including POP and SUI surgery involving mesh and non-mesh repairs. Prior to becoming employed by Ethicon, these surgeons underwent education and training in these areas and had experience in performing these surgeries. These surgeons also regularly read the medical literature and attend professional conferences where risks of surgery are discussed. The pertinent risks with use of these devices were communicated to pelvic surgeons via the IFUs and Ethicon professional education based on the expected common knowledge of the pelvic surgeon. Ethicon also held conferences -- called Summit Meetings or Incontinence and Pelvic Floor Summits -- to which it would invite many experienced pelvic floor surgeons. Their purpose was to discuss surgical treatments for prolapse and stress urinary incontinence, their successes, their complications and provide practice tips. These meetings provided a forum where surgeons came together to benefit from each other's experiences and challenges, to discuss their views on the devices, to validate the professional education, and stay up to date with current practice. In the EU there were expert meetings where the devices were discussed in a similar fashion and at those meetings

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Should sacrospinous ligament fixation for the management of pelvic support defects be part of a residency program procedure? The University of Miami experience. Am J Obstet Gynecol. 1998 Feb;178(2):326-9; Kohli N, Walsh PM, Roat TW, Karram MM. Mesh erosion after abdominal sacrocolpopexy. Obstet Gynecol. 1998 Dec;92(6):999-1004; Nicita G. A new operation for genitourinary prolapse. J Urol. 1998;160:741–45; Schettini M, Fortunato P, Gallucci M. Abdominal sacral colpopexy with prolene mesh. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10(5):295-9; Dwyer PL, Carey MP, Rosamilia A. Suture injury to the urinary tract in urethral suspension procedures for stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10(1):15-21; Diana M, Schettini M. Treatment of vaginal vault prolapse with abdominal sacral colpopexy using prolene mesh. Minerva Ginecol. 1999 Sep;51(9):349-53; Fitzgerald MP, Mollenhauer J, Brubaker L. Failure of allograft suburethral slings. BJU Int. 1999 Nov;84(7):785-8; Handa VL, Stone A. Erosion of a fascial sling into the urethra. Urology. 1999 Nov;54(5):923; Colombo M, Vitobello D, Proietti F, Milani R. Randomised comparison of Burch colposuspension versus anterior colporrhaphy in women with stress urinary incontinence and anterior vaginal wall prolapse. BJOG. 2000 Apr;107(4):544-51; Weber AM, Walters MD, Piedmonte MR. Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol. 2000 Jun;182(6):1610-5; Migliari R, De Angelis M, Madeddu G, Verdacchi T. Tension-free vaginal mesh repair for anterior vaginal wall prolapse. Eur Urol. 2000 Aug;38(2):151-5; Clemens JQ, DeLancey JO, Faerber GJ, Westney OL, Mcguire EJ. Urinary tract erosions after synthetic pubovaginal slings: diagnosis and management strategy. Urology. 2000 Oct 1;56(4):589-94; Fitzgerald MP, Mollenhauer J, Brubaker L. The antigenicity of fascia lata allografts. BJU Int. 2000 Nov;86(7):826-8; Demirci F, Yucel O, Eren S, Alkan A, Demirci E, Yildirim U. Long-term results of Burch colposuspension. Gynecol Obstet Invest. 2001;51(4):243-7; Golomb J, Groutz A, Mor Y, Leibovitch I, Ramon J. Management of urethral erosion caused by a pubovaginal fascial sling. Urology. 2001 Jan;57(1):159-60; Tamussino KF, Hanzal E, Kölle D, Ralph G, Riss PA; Austrian Urogynecology Working Group.. Tension-free vaginal tape operation: results of the Austrian registry. Obstet Gynecol. 2001 Nov;98(5 Pt 1):732-6; Kammerer-Doak DN, Rogers RG, Bellar B. Vaginal erosion of cadaveric fascia lata following abdominal sacrocolpopexy and suburethral sling urethropexy. Int Urogynecol J Pelvic Floor Dysfunct. 2002;13(2):106-9; Bradley CS, Morgan MA, Arya LA, Rovner ES. Vaginal erosion after pubovaginal sling procedures using dermal allografts. J Urol. 2003 Jan;169(1):286-7; Nygaard IE, McCreery R, Brubaker L, Connolly A, Cundiff G, Weber AM, Zyczynski H; Pelvic Floor Disorders Network.. Abdominal sacrocolpopexy: a comprehensive review. Obstet Gynecol. 2004 Oct;104(4):805-23; Maher C, Baessler K, Glazener CM, Adams EJ, Hagen S. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD004014.

there was a significant British contingency as urogynecology was a well-defined subspecialty and interest in the field was great. Based on information gleaned at these summits, Surgeon Monographs were composed and made available to pelvic surgeons warning of potential risks. For example, the 2000 TVT Surgeon's Monograph (Attachment 7) was a report from a 17-surgeon panel representing more than 1,200 cases discussing the TVT device, surgery, and TVT studies. It warned of, and discussed, the treatment/management of numerous complications including vaginal bleeding, retropubic hematoma, vaginal and urethral injury, bladder perforations, retention/obstruction, urethral erosion, mesh exposure, mesh excision surer, vascular injuries, bowel perforations, de novo urge incontinence, infection of the mesh, urinary tract infection and device failure. Similarly, the 2007 Prolift Surgeon's Monograph (Attachment 8) warned of, and discussed, treatment and management of numerous complications such as hemorrhage, visceral injury, ureteral obstruction, hemorrhage, hematoma, fistula, infection, urinary retention, mesh exposure, mesh erosion, mesh excision and removal surgery, dyspareunia, vaginal pain, rectal pain and defecatory dysfunction. These monographs were made available by Ethicon to pelvic floor surgeons. In conclusion, despite Ethicon being aware of the potential complications with these urogynecologic devices, the characteristics and clinical data allowed us to conclude that the benefits of use of the devices outweighed these potential adverse events that were well characterized and manageable in the vast majority of cases.

ATTACHMENT 7

2000 TVT Surgeon Monograph

(Provided via a secure share file site, due to file sizes)

ATTACHMENT 8

2007 Prolift Surgeon Monograph

(Provided via a secure share file site, due to file sizes)

Ethicon Attachments

Attachment 3 – Examples of Marketing Literature

Links to currently available examples below

Includes:

- TVT Abbrevo Literature: *Some of the information included is available here*
- TVT Retropubic Literature
- TVT Obturator Literature

Attachment 4 – Instructions for Use

Links to currently available examples below

Includes:

- Gynecare TVT
- Gynecare TVT with abdominal guides
- Gynecare TVT Obturator System
- Gynecare TVT Secur
- Gynecare TVT Abbrevo
- Gynecare TVT Exact
- Gynemesh PS Prolene
- Gynecare Prolift
- Gynecare Prosima
- Gynecare Prolift + M
- Gynemesh M
- Artisyn Y-shaped Mesh

Attachment 5

Please find attached the lists of significant changes to IFUs for currently marketed devices and discontinued devices respectively.

List of significant changes to IFUs for currently marketed devices

Date	Product	Description of Significant Change
1998 - Oct 29, 2004	TVT	Changed: • FROM: **It is not a comprehensive reference to surgical technique for correcting SUI (Stress Urinary Incontinence).** • **TO:** It is not a comprehensive reference to surgical technique for correcting SUI (Stress Urinary Incontinence) specifically in implanting the device. • WARNINGS & PRECAUTIONS section - 2 additional bullets added 14th and 18th.
Oct 29, 2004	TVT	Changed in EU Notified Body triggering change to CE-Mark from CE0123 to CE0086
Nov 28, 2014	TVT	Add risk of reuse statement in WARNING section: "*Reuse of this device (or portions of this device) may create a risk of product degradation and cross-contamination, which may lead to infection or transmission of bloodborne pathogens to patients and users.*"
Sep 17, 2015	TVT	Current Revision: Alignment with Health Canada Section 39 request (03/24/2014) / FDA proposed rule (05/01/2014) changes that are being initiated to update the global Instructions for Use (IFUs) Changes: • Updates to Warnings and Precautions • Updates to Patient Factors • Updates to Adverse Reactions • Caution copy in Symbology legend changed. • Additional information for device description section
Dec 3, 2001	TVT with Abdominal Guides	Original
Dec 11, 2006	TVT with Abdominal Guides	Changed in EU Notified Body triggering change to CE-Mark from CE0123 to CE0086
Nov 28, 2014	TVT with Abdominal Guides	Add risk of reuse statement in WARNING section: "*Reuse of this device (or portions of this device) may create a risk of product degradation and cross-contamination, which may lead to infection or transmission of bloodborne pathogens to patients and users.*"

Date	Product	Description of Significant Change
Sep 17, 2015	TVT with Abdominal Guides	Current Revision: Alignment with Health Canada Section 39 request (03/24/2014) / FDA proposed rule (05/01/2014) changes that are being initiated to update the global Instructions for Use (IFUs) Changes: • Updates to Warnings and Precautions • Updates to Patient Factors • Updates to Adverse Reactions • Caution copy in Symbology legend changed. • Additional information for device description section
Feb 23, 2010	TVT Exact	Original Release
Nov 28, 2014	TVT Exact	In Warning and Precaution section revise the sentence: FROM: Do not resterilize the GYNECARE TVT EXACT™ Continence System. TO: Do not resterilize/reuse the GYNECARE TVT EXACT™ Continence System. Reuse of this device (or portions of this device) may create a risk of product degradation, which may result in device failure and/or cross-contamination, which may lead to infection or transmission of blood-borne pathogens to patients and users. In Description section of Spanish language: The Implant is approximately 0.027 inches (0.7 mm) thick. The measurement for the thickness of the mesh is being revised in Spanish to reflect mm from 0,7 cm to 0,7 mm. In symbology table, revise description of Caution symbol to read: Caution: See instructions for use. In symbology table, add temperature symbol to be compliant with BS EN ISO 15223-1:2012.
Sep 17, 2015	TVT Exact	Current Revision Alignment with Health Canada Section 39 request (03/24/2014) / FDA proposed rule (05/01/2014) changes that are being initiated to update the global Instructions for Use (IFUs). • Updates to Warnings and Precautions • Updates to Patient Factors • Updates to Adverse Reactions • Caution copy in Symbology legend changed.

Date	Product	Description of Significant Change
Nov 17, 2003	TVT Obturator	Original
Nov 20, 2004	TVT Obturator	Changed in EU Notified Body triggering change to CE-Mark from CE0123 to CE0086
Nov 22, 2005	TVT Obturator	The text in the following numbers in the INSTRUCTIONS FOR USE section have been revised. Numbers 3, 6, 7, 13, 14, 17
June 8, 2010	TVT Obturator	Addition of "Risk of Reuse" statement
June 20, 2014	TVT Obturator	Move Risk of reuse statement from How Supplied to WARNING section: "Reuse of this device (or portions of this device) may create a risk of product degradation and cross-contamination, which may lead to infection or transmission of bloodborne pathogens to patients and users."
Sep 17, 2015	TVT Obturator	Current Revision: Alignment with Health Canada Section 39 request (03/24/2014) / FDA proposed rule (05/01/2014) changes that are being initiated to update the global Instructions for Use (IFUs) Changes: • Updates to Warnings and Precautions • Updates to Patient Factors • Updates to Adverse Reactions • Caution copy in Symbology legend changed. • Additional information for device description section
Apr 15, 2010	TVT Abbrevo	Original
Jul 15, 2010	TVT Abbrevo	Per US FDA's request in order to make the presentation of safety information more prominent in the labeling, the sections titled contraindications, warnings, precautions, adverse reaction & actions have been relocated beneath the Indication section.
May 7, 2015	TVT Abbrevo	Current Revision Alignment with Health Canada Section 39 request (03/24/2014) / FDA proposed rule (05/01/2014) changes that are being initiated to update the global Instructions for Use (IFUs). • Updates to Warnings and Precautions • Updates to Patient Factors • Updates to Adverse Reactions • Caution copy in Symbology legend changed.

Date	Product	Description of Significant Change
Apr 8, 2002	Gynemesh PS	Original
Mar 8, 2003	Gynemesh PS	In ADVERSE REACTIONS section, the word "erosion" has been added.
May 13, 2005	Gynemesh PS	In ADVERSE REACTIONS section, add the statement and scarring that results in implant contraction.
Feb 28, 2013	Gynemesh PS	Updated per US FDA requirements. • Revise Indication for Use statement to limit placement of mesh using abdominal approach only. • Add **Read Carefully** and **Caution** statements to be consistent with order in which this information is presented in the IFU as compared to other more recently FDA cleared mesh products • Expand Contraindications, Warnings, Precautions, Adverse Reaction sections to be consistent with other more recently FDA cleared mesh products used to treat pelvic organ prolapse. • For clarity, expand Use Instructions, Sterility and Storage information sections. • Add Risk of reuse statement to Sterility section. • Device Description sections – last sentence deleted to be consistent with Device Description of other more recently FDA cleared mesh products. • Added Disposal section to be consistent with other more recently FDA cleared mesh products • Expanded How Supplied section to describe two sizes of mesh available •
Feb 3, 2015	Gynemesh PS	Current Revision Comply with a Request for Additional Information under Section 39 of the Medical Device Regulations Health Canada (HC) and the FDA Proposed Rule FR Publication. Changes to: 1) Add / edit content under Adverse Reactions section 2) Add PATIENT FACTORS section

Date	Product	Description of Significant Change
June 3, 2014	Artisyn	Add : - Enhanced Risk of Reuse as last bullet under Warnings section - Update storage section to read: Recommended storage conditions: at or below 30C (86F). - Do not use after expiry date.
Jan 20, 2015	Artisyn	Current Revision Comply with a Request for Additional Information under Section 39 of the Medical Device Regulations Health Canada 1) Add / edit content under Adverse Reactions section 2) Add PATIENT FACTORS section

List of significant changes to IFUs for discontinued devices

Date	Product	Description of Significant Change
Nov. 30, 2005	TVT Secur	Original
Nov. 6, 2007	TVT Secur	Latest revision Inaccuracies in German translation corrected.
Dec. 17, 2004	PROLIFT	Original
Dec. 10, 2008	PROLIFT	Changes made to align with 1) IFU draft submitted to FDA and discussions with the FDA with regard to the Prolift 510k (510k clearance received 5/16/08); and 2) Harmonization with PROSIMA and PROLIFT +M labelling.
Jun. 8, 2010	PROLIFT	Latest revision Added risk of reuse statement "Reuse of this device (or portions of this device) may create a risk of product degradation and cross-contamination, which may lead to infection or transmission of bloodborne pathogens to patients and users."
Feb. 23, 2007	PROSIMA	Original
May 18, 2007	PROSIMA	Typographical revisions and minor illustration updates.
May 28, 2010	PROSIMA	Latest revision Added risk of reuse statement "Reuse of this device (or portions of this device) may create a risk of product degradation and cross-contamination, which may lead to infection or transmission of bloodborne pathogens to patients and users."
Jun. 1, 2010	Gynemesh M	Original
Jan. 29, 2013	Gynemesh M	Latest revision No significant changes.
Jun. 24, 2008	PROLIFT +M	Original
Jun. 10, 2010	PROLIFT +M	Latest revision: Added risk of reuse statement "Reuse of this device (or portions of this device) may create a risk of product degradation and cross-contamination, which may lead to infection or transmission of bloodborne pathogens to patients and users."

Attachment 7

Klutke, C., Kuhn, E., Lucente, V. (2000) Surgeons' Resource Monograph: expert opinion on the use of Gynecare TVT tension-free support for incontinence. Ethicon Inc.

Attachment 8

(unknown) (2007) Surgeons' Resource Monograph on Gynecare Prolift Pelvic Floor Repair Systems. Ethicon Inc.

FEG Textiltechnik

COI:

As manufacturer of mesh implants we are an active economic operator. We develop and manufacture all our mesh implants in Aachen, Germany. We have our own fully integrated production line to manufacture our products from polymer granule right up to the final product. This enables full quality control along the entire production chain. As an independent owner-managed SME we are not subjected to any investors' expectations. Thus, we can afford to focus on safe and effective products. Only in this light it was possible to establish the superior polymer PVDF as implant material for mesh implants.

Submission:

23rd of October 2018

As manufacturer of **DynaMesh®** Implants for Pelvic Floor Reconstruction and Treatment of Urinary Incontinence, made by FEG Textiltechnik mbH in Aachen, we would like to come back to you regarding the call for evidence.

To answer the questions in this call for evidence in a clear way it is very helpful to cluster our product range as follows:

I Implants for transvaginal pelvic floor repair

II Implants for incontinence treatment

III Implants for abdominal pelvic floor repair
- IIIa unilateral suspension
- IIIb bilateral suspension

1. **Please confirm the synthetic mesh products that you market or have previously marketed within the EU for use in urogynaecological surgery.**

   The market and previously marketed products are:

   <u>Product group I:</u> Transvaginal mesh Implants for prolapse repair
   DynaMesh®-PR4 range for the anterior repair
   DynaMesh®-PR2 range for the posterior repair

   <u>Product group II:</u> Implants for incontinence treatment – suburethral (retropubic / transobturatoric)
   DynaMesh®-SIS range with reusable instruments for the retropubic approach
   DynaMesh®-RSUS range with disposable instruments for the retropubic approach
   DynaMesh®-SIS direct range with reusable instruments for the transobturatoric approach
   DynaMesh®-TSUS range with disposable instruments for the transobturatoric approach
   DynaMesh®-SIS minor without instruments for an minimal invasive approach (out of market)

   <u>Product group III:</u> Implants for pelvic floor repair abdominally (laparotomy / laparoscopy)
   Product group IIIa: Unilateral suspension:
   DynaMesh®-PR range for single sided sacrocolpopexy / hysteropexy

DynaMesh®-PRS range range for double sided sacrocolpopexy

Product group IIIb: Bilateral suspension
DynaMesh®-PRP range for pectopexy
DynaMesh®-CESA range for bilateral cervical sacropexy
DynaMesh®-VASA range for bilateral vaginal sacropexy

2. Please detail for each such device:

a) Premarket testing undertaken;
All our products were developed under full compliance with the legal regime at this time which did not inevitably claimed any premarket testing. These developments are described in the Design Control Files for each product, including the description of premarket testing as bench tests, textile testing, biological and toxicological test according to ISO 10993. Whenever the risk-benefit consideration results in the necessity of further preclinical testing, such tests were carried out. These tests include not only in-vitro tests but also cadaver and/or animal trials.

b) any clinical evaluation undertaken;
The clinical evaluation for all of our products is based on the equivalence assessment in full compliance with the legal regime of the medical device directive (Council Directive 93/42/EEC). The core elements of these clinical evaluations are the equivalence assessment itself, the risk assessment according to the ISO standard 14971 and the clinical evaluation report.
According to our company policies and beyond the scope of the legal regime, we established an additional evaluation phase subsequent to CE approval. Each of our products first was given (for a defined trial period) to a predefined circle of users, including the user which were involved in the product development. Only after positive evaluation of the products during this evaluation phase and expected/satisfying clinical outcome during that trial period, the products were launched on the market.
After the product launch the clinical evaluation continued by means of our post market surveillance system which does not only include the assessment and analysis of each feedback from the market but also systematic data records under the scope of post market studies. A selection of ongoing studies is given below:

Titel of Study	**n**	**Current status**	**Principle Investigator**
CESA/VASA retrospectiv Study with DynaMesh®CESA and /-VASA	500	Publication in 2019	Kirschner Hermanns (GER)
CESA/VASA – Hysteropexy with DynaMesh®-CESA	30	Follow up ongoing	Joszwik (PL)
Pectopexy Study – prospective with DynaMesh®-PRP soft	500	Follow up ongoing	Noè (GER)
Pectopexy Study – retrospective with	500	In preperation	Anapolski (GER)

DynaMesh®-PRP soft and /-PR			
POP-reconstruction anterior compartiment plus cervicosacropexy with DynaMesh®PRS visible	130	In preperation	Kociszweski (GER)
DynaMesh®-SIS soft prospective follow up study	100	Follow up ongoing	Mukhopadhyay (UK)

A selection of publications as results of i. a. PMS activities are listed below:

Publication with respect to product group I:
Göretzlehner U, Müllen A: PVDF as an Implant Material in Urogynaecology Interdisciplinary Journal of Functional Materials, Biomechanics and Tissue Engineering BIOmaterialien 8(S1): 28-29., ISSN 1616-0177; © Neuer Merkur GmbH, Munich (2007)

Kaldenhoff E, Klinge U, Klosterhalfen B, Najjari L, Maass N: Von der Prolaps- zur Problempatientin: Schenken wir der Qualität von Netzimplantaten genügend Aufmerksamkeit? Der Gynäkologe 46, Nr. 7 (Juli 2013): 469–76

Barski D, Arndt C, Gerullis H, Yang J, Boros M, Otto T, Kolberg H C: Transvaginal PVDF-Mesh for Cystocele Repair: A Cohort Study International Journal of Surgery 39 (März 2017): 249–54

Publication with respect to product group II:
Klinge U, Binnebösel M, Kuschel S, Schüssler B: Demands and Properties of Alloplastic Implants for the Teatment of Stress Urinary Incontinence. Expert Review of Medical Devices 4/3: 349-359, DOI 10.1586/17434440.4.3.349; © Future Drugs Ltd., Austria (2007)

Otto J, Kaldenhoff E, Kirschner-Hermanns R, Mühl T, Klinge U: Elongation of Textile Pelvic Floor Implants under Load is Related to Complete Loss of Effective Porosity, thereby Favouring Incorporation in Scar Plates. Journal of Biomedical Materials Research Part A 102/4: 1079-84, DOI 10.1002/jbm.a.34767; © Wiley Periodicals, Inc. (2013)

Najjari L, Gräf C M, Kupec T, Stickeler E, Goecke T W, Meinhold-Heerlein I: Tomographic Ultrasound Imaging to Control the Placement of Tension-Free Transobturator Tape in Female Urinary Stress Incontinence. BioMed Research International 2016 (2016): 1–6

Naumann G, Albrich S, Skala C, Laterza R, Kölbl H: Single-Incision Slings (SIS) - a New Option for the Surgical Treatment of Female Stress Urinary Incontinence. Geburtshilfe und Frauenheilkunde 72/02: 125–31, DOI 10.1055/s-0031-1298275; © Georg Thieme Verlag KG (2013)

Ludwig S, Stumm M, Mallmann P, Jager W: Surgical replacement of the uterosacral-and pubourethral-ligaments as treatment for urgency urinary incontinence Austin J Womens Health 3, Nr. 1 (2016): 1019

Ludwig S, Stumm M, Mallmann P, Jager W: TOT 8/4: A Way to Standardize the Surgical Procedure of a Transobturator Tape BioMed Research International 2016 (2016): 1–4

Najjari L, Hennemann J, Kirschner-Hermanns R, Maass N, Papathemelis T: Visualization of Polypropylene and Polyvinylidene Fluoride Slings in Perineal Ultrasound and Correlation with Clinical Outcome Research article. BioMed Research International, 2014

Roman S, Urbánková I, Callewaert G, Lesage F, Hillary C, Osman N I, Chapple C R, Deprest J, MacNeil S: Evaluating Alternative Materials for the Treatment of Stress Urinary Incontinence and Pelvic Organ Prolapse: A Comparison of the In Vivo Response to Meshes Implanted in Rabbits. The Journal of Urology 196, Nr. 1 (Juli 2016): 261–6947

Sabadell J, Larrain F, Gracia-Perez-Bonfils A, Montero-Armengol A, Salicrú S, Gil-Moreno A, Poza J L: Comparative Study of Polyvinylidene Fluoride and Polypropylene Suburethral Slings in the Treatment of Female Stress Urinary Incontinence: PVDF/Polypropylene in Suburethral Slings. Journal of Obstetrics and Gynaecology Research 42, Nr. 3 (März 2016): 291–96

Publication with respect to product group III:

Noé K, Spüntrup C, Anapolski M: Laparoscopic Pectopexy: A Randomised Comparative Clinical Trial of Standard Laparoscopic Sacral Colpo-Cervicopexy to the New Laparoscopic Pectopexy. Short-term Postoperative Results. Archives of Gynecology and Obstetrics 287: 275–280, DOI 10.1007/s00404-012-2536-7; © Springer-Verlag (2012)

Jäger W, Mirenska O, Brügge S: Surgical Treatment of Mixed and Urge Urinary Incontinence in Women Gynecologic and Obstetric Investigation 74/2: 157–64, DOI 10.1159/000339972; © S.Karger AG, Basel (8/2012)

Noé K, Schiermeier S, Alkatout I, Anapolski M: Laparoscopic Pectopexy: A Prospective, Randomized, Comparative Clinical Trial of Standard Laparoscopic Sacral Colpocervicopexy with the New Laparoscopic Pectopexy-Postoperative Results and Intermediate-Term Follow-Up in a Pilot Study - Short-term Postoperative Results. Journal of Endourology. ahead of print. doi:10.1089/end.2014.0413; © Mary Ann Liebert, Inc. (2014)

Jager W, Ludwig S, Mallmann P: Does the Patients Age have an Influence on the Outcome of Cesa (Cervico-Sacropexy) and Vasa (Vagino-Sacropexy) for the Treatment of Urinary Incontinence in Women? J Gerontol Geriatr Res 5/1 : 277. DOI 10.4172/2167-7182.1000277; © J Gerontol Geriatr (2016)

Rajshekhar S, Mukhopadhyay S, Morris E: Early Safety and Efficacy Outcomes of a Novel Technique of Sacrocolpopexy for the Treatment of Apical Prolapse International Journal of Gynecology and Obstetrics 0, Nr. 0 (25. Juli 2016)

Joukhadar R, Meyberg-Solomayer G, Hamza A, Radosa J, Bader W, Barski D, Ismaeel F, Schneider G, Solomayer E, Baum S: A Novel Operative Procedure for Pelvic Organ

Prolapse Utilizing a MRI-Visible Mesh Implant: Safety and Outcome of Modified Laparoscopic Bilateral Sacropexy. BioMed Research International 2015 (2015): 1–9

Balsamo R, Illiano E, Zucchi A, Natale F, Carbone A, De Sio M, Costantini E: Sacrocolpopexy with Polyvinylidene Fluoride Mesh for Pelvic Organ Prolapse: Mid Term Comparative Outcomes with Polypropylene Mesh. European Journal of Obstetrics & Gynecology and Reproductive Biology 220 (Januar 2018): 74–78

Ludwig S, Stumm M: Surgical Treatment of Urgency Urinary Incontinence, OAB (Wet), Mixed Urinary Incontinence, and Total Incontinence by Cervicosacropexy or Vaginosacropexy Gynecology & Obstetrics 6, Nr. 9 (2016)

Kale A, Biler A, Terzi H, Usta T, Kale E: Laparoscopic pectopexy: initial experience of single center with a new technique for apical prolapse surgery.International braz j urol 43, Nr. 5 (Oktober 2017): 903–9

Urbankova I, Sindhwani N, Callewaert G, Turri A, Rita R, Hympanova L, Feola A, Deprest J: In Vivo Documentation of Shape and Position Changes of MRI-Visible Mesh Placed in Rectovaginal Septum. Journal of the Mechanical Behavior of Biomedical Materials 75 (November 2017): 379–89

Publication with respect to the material PVDF and the effect of shrinkage:

Klinge U, Klosterhalfen B, Öttinger A P, Junge K, Schumpelick V: PVDF as a new Polymer for the Construction of Surgical Meshes. Biomaterials 23/16: 3487-3493; © Elsevier, NL (2002)

Klink C D, Junge K, Binnebösel M, Alizai H P, Otto J, Neumann U P, Klinge U: Comparison of Long-Term Biocompatibility of PVDF and PP Meshes. Journal of Investigative Surgery, 24: 292-299, DOI 10.3109/08941939.2011.589883; © Informa Healthcare, Inc. USA (2011)

Silva, R.A., Silva, P.A., Carvalho, M.E., 2007. Degradation studies of some polymeric biomaterials: Polypropylene (PP) and polyvinylidene difluoride (PVDF), in: Chandra, T., Tsuzaki, K., Militzer, M., Ravindran, C. (Eds.), THERMEC 2006, Pts 1-5. Trans Tech Publications Ltd, Stafa-Zurich, pp. 573–576.

Gerullis H, Georgas E, Eimer C, Goretzki P E, Lammers B J, Klosterhalfen B, Borós M, Wishahi M, Heusch G, Otto T: Evaluation of Biocompatibility of Alloplastic Materials: Development of a Tissue Culture in Vitro Test System Surgical Technology International XXI; © Universal Medical Press, Inc. USA (2012)

Gerullis H, Klosterhalfen B, Borós M, Lammers B, Eimer C, Georgas E, Otto T: IDEAL in Meshes for Prolapse, Urinary Incontinence, and Hernia Repair Surgical Innovation OnlineFirst XX, pp 1-7, DOI 10.1177/1553350612472987; © sage publications (2013)

Laroche G, Marois Y, Schwarz E, Guigoin R, King M W, Pâris E, Douville Y: Polyvinylidene Fluoride Monofilament Sutures: Can They Be Used Safely for Long-Term Anastomoses in the Thoracic Aorta? Artificial Organs 19/11: 1190-1199; © Blackwell Science, Inc., Boston (12/1995)

Mühl T, Binnebösel M, Klinge U, Goedderz T: New Objective Measurement to Characterize the Porosity of Textile Implants. Journal of Biomedical Materials Research Part B: Applied Biomaterials: 176-183, DOI 10.1002/jbmb; © Wiley Periodicals, Inc. (5/2007)

Muysoms, F., Beckers, R., Kyle-Leinhase, I., 2017. Prospective cohort study on mesh shrinkage measured with MRI after laparoscopic ventral hernia repair with an intraperitoneal iron oxide-loaded PVDF mesh. Surgical Endoscopy. https://doi.org/10.1007/s00464-017-5987-x

Sindhwani N, Liaquat Z, Urbankova I, Vande Velde G, Feola A, Deprest J: Immediate Postoperative Changes in Synthetic Meshes – In Vivo Measurements. Journal of the Mechanical Behavior of Biomedical Materials 55 (März 2016): 228–3

Sindhwani N, Feola A, De Keyzer F, Claus F, Callewaert G, Urbankova I, Ourselin S, D'hooge J, Deprest J: Three-Dimensional Analysis of Implanted Magnetic-Resonance-Visible Meshes International Urogynecology Journal 26, Nr. 10 (Oktober 2015): 1459–65

c) whether conformity was declared on the basis of equivalence to an existing device, and if so, please detail the existing device;

Conformity for all our products was declared on the basis of equivalence and in full compliance with the legal regime of the medical device directive (Council Directive 93/42/EEC). Equivalence is demonstrated both to our own products and/or to competitor products.

A list of the most relevant competitor products which were involved in the equivalence assessment is given below. Again, the list is structured according to the product groups as defined previously:

	Product name of the equivalent product	Manufacturer of the equivalent product
Product group I	*AMS* Perigree	American Medical Systems
	AMS Apogee	American Medical Systems
	GYNECARE P*rolift*	J&J/*Ethicon*
Product group II	GYNECARE TVT	J&J/*Ethicon*
	GYNECARE TVT Obturator	J&J/*Ethicon*
	Serasis	Serag Wiesner
Product group III	GYNECARE GYNEMESH PS	J&J/Ethicon
	Tiloop	Pfm Medical
	ALYTE Y-Mesh	Bard Medical

d) specify the notified body used for the conformity assessment, and the date the conformity assessment was undertaken;

ecm Zertifizierungsgesellschaft für Medizinprodukte in Europa GmbH, Bismarckstr. 106, 52066 Aachen, Germany.
CE-Certificate: ISO 13485 / 9001 - December 9th, 2015
CE-Zertifikat: RL-93-42-EWG-en - December 5th, 2014

e) date of CE marking;

	first product with CE	
Product group I	Name of Product:	DynaMesh®-PR2

	Date of conformity decl.:	DynaMesh®-PR4 03.04.2006
Product group II	Name of Product: Date of conformity decl.:	DynaMesh®-SIS DynaMesh®-SIS direct 25.10.2005
Product group III	Name of Product: Date of conformity decl.:	DynaMesh®-PR 03.04.2006

f) any changes to the design;

The initiation to make any change to the design is driven by the results of the PMS-system. Down to the present day, none of our products needed any change to the design subsequent to the market launch. Minor changes to packaging or labelling reflects optimized usability or regulatory requirements.

g) any changes to the indications (please detail);

Down to the present day none of our products needed any change to the indications.

h) date of removal from market in the UK and worldwide if applicable, and reasons for this;

Down to the present day none of our products was removed from the market. However, one product will be removed from the market worldwide in the near future: DynaMesh®-SIS minor. The decision to remove the product is clearly and only driven by a portfolio cleanup based on a business decision. The reason to remove the product is in no way affected by an undesired clinical results and will not be carried out under the scope of a Field Safety Corrective Action – FSCA. At this time we have another product on the market that implicated the indication of the DynaMesh®-SIS minor.

i) if the device continued to be marketed elsewhere in the world.

The product DynaMesh®-SIS minor will be removed from the market worldwide in the near future.

3. Can you describe the marketing strategy for each device and provide examples of the marketing literature used? For each device, please can you include any instructions for use including details of changes over time.

The marketing strategy for all our products is based on three aspects:

1. Sales specialists: We develop and manufacture mesh implants however, we do not have a direct sales force. Instead, we have partnerships with specialized local medical device distributors to provide the products to the end-users in certain markets. The distributors are selected carefully according to a strict set of criteria. To ensure that the distributors represent our products as product specialists we train the distributor's staff carefully and regular according to a defined training program.
2. Physician training centres: We request and support the setup of training centres to train physicians in the correct use of our products in each of the countries in which we are represented. Training centres are an excellent way to bring and to keep procedures performed with our products up to a high standard.
3. Catalogue information: We provide detailed information about all our products in general, about the product features, about the product characteristics and about the material the products are made of.

Please find enclosed the current product catalogue "Female Urinary Incontinence and Pelvic Floor Descent" in which all our products are described.

Further, please find enclosed the IFU for each of our products. The initiation to make any change to the IFU is driven by the results of the PMS-system and/or by regulatory requirements. Down to the present day, none of our products needed any essential change to the IFU subsequent to the market launch.

4. **Please provide details of device traceability for example Unique Device Identifiers, shelf life and reason(s) for that shelf life, batch traceability, and batch and product recall.**
   Labelling for all our products is in full compliance with the legal regime of the medical device directive (Council Directive 93/42/EEC).
   Device traceability: Traceability of the products is ensured by means of the reference number and the lot number. Both numbers are given on the product package as well as on a set of stickers which are also used to label the DynaMesh®-Implant passport which will be kept by the patient. Our distributors are obliged by contract to keep the distribution record and to ensure an appropriate level of traceability of our devices. By means of the traceability we can ensure the effectiveness of the post-market safety-related activities as field safety corrective actions.
   Shelf life and reason(s) for that shelf life: We ensure a shelf life of 5 years. Material tests following standard test settings have substantiated a shelf life of at least 7 years without any measurable impact on packaging, sterility and product quality. Taking a safety margin of 30% into account results in a shelf life of 5 years.
   Batch and product recall:
   In case of a recall we follow the procedural instruction “recall” as part of our quality management system.

5. **Please share any evidence of positive feedback on pelvic mesh from clinicians or patient groups.**
   As part of our PMS-system both manufacturer’s employees as well as distributor’s employees are in regular direct contact with end-users of our products, either during daily sales activities, during trainings or during congresses and/or symposia. Each PMS analysis down the present day results in a predominant positive feedback for each of our products.

6. **For each device, please specify the composition of the materials and changes over time.**
   All our products are made of pure, medical grade Polyvinylidenfluorid (PVDF). PVDF has been known to be an extremely ageing-resistant polymer with excellent biocompatibility. PVDF has been used for decades for sutures in delicate applications such as cardiac or ophthalmic surgery. Furthermore, it has been used successfully in textile implants since 2002.

7. **Please can you provide sales data for each device, and if known, market share.**

	Total sales [pc.] 2006 till 2017
Product group I	> 6.500
Product group II	> 36.500
Product group III	> 19.500

8. **Please provide details of any post-marketing vigilance studies of relevance to the Review, including 522 studies if appropriate.**

The initiation to conduct a post market clinical follow up study (PMCF-study) is driven by the results of the PMS-system. Down to the present day, the PMS results did not indicate the necessity to conduct a PMCF-study.

9. **Please can you supply a summary of in-vivo shrinkage data relevant to your products.**
As manufacturer of mesh implants we provide implants not only for the treatment of urinary incontinence and pelvic floor descent but also for hernia treatment. The effect of in-vivo shrinkage is an issue of interest for each mesh application. Thus, we developed a sophisticated and unique technology that enables the assessment of in-vivo shrinkage to any surgeon in the world who uses our visible products: DynaMesh® visible Technology. The visible technology is based on the incorporation of MRI sensitive iron oxide micro particles into the polymer matrix. By means of the markers the mesh implants are visible via MRI. We could successfully prove that our PVDF implants are subjected to a minimal in-vivo shrinkage (~ 7,5%) which we ascribe to the superior biocompatibility of PVDF and to the sophisticated mesh design (high effective porosity): A prospective study on mesh shrinkage using the DynaMesh®-visible Technology results in an in-vivo shrinkage of 6.5% comparing the original mesh size and the mean calculated surface area 3 months postoperatively.[1] Another prospective cohort study on mesh shrinkage using the DynaMesh®-visible Technology results in a surface area shrinkage of 1.0% for the surface area of the mesh between 1 and 13 months.[2] A similar surface area shrinkage of less than 2.0% was measured in a DynaMesh® PR4 visible mesh between 6 weeks and 8 months post implantation. [3]

10. **Please could you provide a timeline outlining your understanding and recognition of risks regarding the use of synthetic polymer mesh in pelvic surgery. This may include: initial recognition of the risk, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients.**
We have been closely following the developments in that therapeutic area of transvaginal mesh surgery, in particular since the release of the official FDA warning on transvaginal mesh erosions due to excessive scar tissue formation in 2008. The concerns raised by the FDA were explicitly taken into account during development of our products by firstly choosing the material polyvinylidene fluoride (PVDF) and by secondly designing of mesh structures adopted to the individual requirements with focus on the effective porosity.
All meshes that are accused of having high rates of adverse effects, e.g. erosion, have been manufactured from polypropylene (PP). All urogynaecological meshes manufactured by FEG are made from the material PVDF, which has been proven to show reduced scar tissue formation. In a report by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), the European Commission calls for novel, improved materials for urogynaecological mesh implants and explicitly mentions PVDF as a promising synthetic material for urogynaecological meshes. In a statement issued by the International Urogynecological Association (IUGA) on this report, PVDF is highlighted for its reduced foreign body reaction, increased elasticity, and long-term stability.

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[1] Köhler, G. et al. First human magnetic resonance visualisation of prosthetics for laparoscopic large hiatal hernia repair. Hernia (2015). doi:10.1007/s10029-015-1398-x

[2] Muysoms, F., Beckers, R. & Kyle-Leinhase, I. Prospective cohort study on mesh shrinkage measured with MRI after laparoscopic ventral hernia repair with an intraperitoneal iron oxide-loaded PVDF mesh. Surgical Endoscopy (2017). doi:10.1007/s00464-017-5987-x

[3] Nikhil Sindhwani u. a., „Three-Dimensional Analysis of Implanted Magnetic-Resonance-Visible Meshes“, *International Urogynecology Journal*, 24. März 2015, 1–7, https://doi.org/10.1007/s00192-015-2681-1.

There are only two meshes for transvaginal surgery manufactured by FEG. These have been designed from the start to minimise the amount of mesh-material needed for reconstructive surgery and therefore, to avoid the problems that led to some manufacturers retracting their products from the market.

11. **Please can you provide details of your relevant policies and protocols, if any, for ensuring that information relevant to patient safety, and learning from adverse events is disseminated.**
    The recording, analysis and dissemination of these information is described in the procedural instruction "post marketing surveillance and vigilance" as part of our quality management system. Based on statistical methods we ensure to identify trends on short and long term both regarding a single product but also across all products.

12. **Please describe the steps you take in your post-marketing vigilance, and any policies you've introduced to recognise and respond to events proactively.**
    In case of any event we follow the procedural instruction "complaints" as part of our quality management system. This includes: Whenever a patient is involved into the complaint members of the department clinical affairs contact the end-user to request detailed information about the case which enables us to assess the case with respect of a potential mesh relation. In case of doubt external experts are involved into the assessment procedure. We consider registers as one of the most effective tools for a comprehensive and reliable market surveillance to recognize events. Thus, we support any activity of already established registers and at the same time we are working on the establishment of our company own register.

13. **Please can you supply a summary of adverse event reports, with dates of receipt but fully anonymised, related to use of synthetic mesh in pelvic surgery.**

	sales [pc.] 2006 - 2017	**number/dates of adverse events - clearly not mesh related**		**number/dates of adverse events - potentially mesh related**		**number/dates of adverse events - clearly mesh related**	
Product group I	> 6.500	0	-	0	-	0	-
Product group II	> 36.500	0	-	0	-	0	-
Product group III	> 19.500	0	-	0	-	0	-

In addition, please find below also the summary of <u>feedback from the market</u>, with dates of receipt

	sales [pc.] 2006 - 2017	**number/dates of feedback from market with administrative background**		**number/dates of feedback from the market with clinical background**	
Product group I	> 6.500	0		1	16.2.2016
Product group II	> 36.500	2	17.11.2010 24.2.2011	3	20.1.2009 22.10.2009 21.9.2010
Product group III	> 19.500	0		1	6.7.2016

14. **In your view, where within the healthcare system does your corporate responsibility lay for disseminating and responding to adverse event reporting begin and end?**
    As manufacturer, our corporate responsibility within the healthcare system for disseminating and responding to adverse event reporting starts with a comprehensive and reliable market surveillance including the recording of all available information both passively or actively collected. It continues with the analyses and assessment of all information and ends with the notification of authorities and the accomplishment of a Field Safety Corrective Action – FSCA, when appropriate.

15. **Who has the final say on what should be included on the data sheets and patient information leaflets? If you have exceeded the minimum requirements specified by the regulator please provide details.**
    All patient information leaflets are prepared in cooperation between the departments R&D and clinical affairs, with the final say at clinical affairs.

16. **Please can you describe the elements of your corporate social responsibility policy which relate to the availability of products, and the risk-benefit analysis for products that you manufacture?**
    According to our understanding of our social responsibility we have the policy "PATIENTS SAEFTY FIRST". The vast majority of products were moreover developed - and made available to use - entirely in close cooperation with experienced clinicians.
    Based on this strict policy we came to the conclusion – in spite of economic disadvantages – to produce our female pelvic health implants out of PVDF in spite of Polypropylene. This decision was purely made because of the above policy and the fact, that PVDF has superior characteristics for the use in the human body.

17. **If applicable, please can you provide a brief summary of litigation and/or settlements relevant to your product(s), both within the UK and worldwide?**
    Up to the present day we never were involved in any litigation and/or settlements relevant to your product(s), both within the UK and worldwide.

18. **Do you contribute to an administrative (non-litigative) redress scheme anywhere in the world, such as the Nordic pharmaceutical insurance schemes?**
    If so, where, and what are the terms of the contribution?
    What is your evaluation of the scheme?
    -no-

Please explain the basis for the evidence you are submitting to the Review, how that evidence was selected, the extent to which any relevant material has been withheld and the reasons why.
All information given in this report are based on the current version of our quality management system and our technical documentation for the products. Evidence was selected with the proviso of reliability and effectiveness. We had no reasons to withhold any relevant information.

Please detail any commercial, financial or legal connection or interest in the pharmaceutical and medical devices industry sector (including subsidiaries) or any other body or organisation of interest to the Review.

As manufacturer of mesh implants we are an active economic operator. We develop and manufacture all our mesh implants in Aachen, Germany. We have our own fully integrated production line to manufacture our products from polymer granule right up to the final product. This enables full quality control along the entire production chain. As an independent owner-managed SME we are not subjected to any investors' expectations. Thus, we can afford to focus on safe and effective products. Only in this light it was possible to establish the superior polymer PVDF as implant material for mesh implants.

You may also want to suggest any potential questions that you would like asked of others who may be giving evidence to the Review.

1) What is/are the rationale/reasons to select the proper implant material (purity, long term resistance, intensity of foreign body reaction)
2) What are the critical product characteristics which meet the individual requirements for each indication (porosity, mechanical properties)
3) Which imaging solutions are available to enable a postoperative assessment of the proper product positioning and functioning (in-vivo behaviour)

Additional statement
As part of the reply to question 12 we elucidated that we consider registers as one of the most effective tools for a comprehensive and reliable market surveillance to recognize events and to improve patient safety. However, the cooperation between established registers and the manufacturers prove difficult. As reason mostly provisions of the European general data protection regulation GDPR are invoked as reason. A less unobstructed access to available data both in cooperation with registers as well as in cooperation with individual health centres will improve the market surveillance quality. Any beneficial suggestion to improve this situation is welcome!

Please confirm that you give permission for that evidence to be used for the purposes of the Review. Any information you choose to provide will be held according to information handling policies which are available on our website, 'How we handle the Information you provide to the Review – Data Protection and Privacy Information' and the 'Anonymity and Redaction Framework'. These can be provided in alternative formats if requested.

We herewith give permission for that evidence to be used for the purposes of the Review.

Sincerely yours
Dr. Boris Obolenski (CEO)

Attachments Provided:

FEG Textiltechnik provided the following attachments. Links are provided to currently available versions.

- **Dynamesh - Female Urinary Incontinence and Pelvic Organ Prolapse**

Instructions for use:

- **Dynamesh -CESA/ -VASA and -CERESA/ -VARESA**
- **Dynamesh – Reusable instruments pelvic floor (female)**

- **Dynamesh -ISR101 and -IST103**
- **Dynamesh -PR/soft/visible, -PRR soft/visible, -PRS soft/visible, -PR2 soft/visible, -PR4 soft/visible**
- **Dynamesh -PRP soft/visible**
- **Dynamesh -SIS, -SIS soft, - SIS visible, -SIS direct, -SIS direct soft, -SIS direct visible**

Medtronic

Thank you for your inquiry dated 19-Sep-2018 regarding the above referenced review. Your questions have been restated in **bold** below, followed by our response.

1. Please confirm the synthetic mesh products that you market or have previously marketed within the EU for use in urogynaecological surgery.

Medtronic no longer manufactures surgical mesh implants intended for transvaginal placement in the repair of pelvic organ prolapse and treatment of stress urinary incontinence.
For convenience of review, we have provided a list of Medtronic products that we previously manufactured through its subsidiaries Sofradim Production (Trevoux, France) and Tissue Science Laboratories (Leeds, United Kingdom), and which have been previously marketed within the EU for use in urogynecological surgery.

Table I

Product name	Manufactured by	Distributed by	Year of first CE-mark	Notified Body	Year of last manufacture
Biologics					
Pelvicol® Surgical Implant	Tissue Science Laboratories	CR BARD	2000	LRQA (0088)	2013
PelviSoft™ Biomesh	Tissue Science Laboratories	CR BARD	2004	LRQA (0088)	2013
Pelvilace®, Pelvilace® TO	Tissue Science Laboratories	CR BARD	2004	LRQA (0088)	2013
Synthetic mesh					
Parietex™ Ugytex™ / Kit	Sofradim Production	COVIDIEN	2002	GMED (0459)	2015
Pelvitex™ / Avaulta™ System	Sofradim Production	CR BARD	2004	GMED (0459)	2009
Parietene Duo™/Quadra™	Sofradim Production	COVIDIEN	2007	GMED (0459)	2011
Parietex™ ProSup™	Sofradim Production	COVIDIEN	1996	GMED (0459)	2016
Uretex™	Sofradim Production	COVIDIEN	2000	GMED (0459)	2015
IVS™, IVS™ Tunneler	Sofradim Production	COVIDIEN	2009	GMED (0459)	2009

2. Please detail for each such device:
a) Premarket testing undertaken;
Surgical mesh implants identified herein were subject to premarket testing in accordance with the applicable requirements of the medical device directive 93/42/EEC and the applicable provisions of the standard ISO 13485, as applicable at the time they were first placed on the market. Such testing typically included – without limited to – biocompatibility testing and mechanical testing.

b) any clinical evaluation undertaken;

We conducted the clinical evaluations in accordance with the medical device directive 93/42/EEC and applicable European MEDDEV guidelines. These clinical evaluations use literature reviews and critical assessment of all the clinical trials on product where available.

c) whether conformity was declared on the basis of equivalence to an existing device, and if so, please detail the existing device;

We consider this as no longer relevant. Surgical mesh implants identified herein are no longer manufactured.

d) specify the notified body used for the conformity assessment, and the date the conformity assessment was undertaken;

Please refer to Table I above.

e) date of CE marking;

Please refer to Table I above.

f) any changes to the design;

We consider this as no longer relevant. Surgical mesh implants identified herein are no longer manufactured.

g) any changes to the indications (please detail);

We consider this as no longer relevant. Surgical mesh implants identified herein are no longer manufactured.

h) date of removal from market in the UK and worldwide if applicable, and reasons for this;

Surgical mesh implants identified herein were not subject to any product recall or removal from the market. Medtronic gradually ceased the manufacturing of these products.

i) if the device continued to be marketed elsewhere in the world.

Surgical mesh implants identified herein are no longer manufactured or marketed.

3. Can you describe the marketing strategy for each device and provide examples of the marketing literature used? For each device, please can you include any instructions for use including details of changes over time.

We consider this as no longer relevant. Surgical mesh implants identified herein are no longer manufactured.

4. Please provide details of device tracibility for example Unique Device Identifiers, shelf life and reason(s) for that shelf life, batch traceability, and batch and product recall.
We consider this as no longer relevant. Surgical mesh implants identified herein are no longer manufactured. Surgical mesh implants identified herein were not subject to any product recall or removal from the market.

5. Please share any evidence of positive feedback on pelvic mesh from clinicians or patient groups.
We consider this as no longer relevant. Surgical mesh implants identified herein are no longer manufactured.

6. For each device, please specify the composition of the materials and changes over time.

Product name	Implanted materials
Biologics	
Pelvicol® Surgical Implant	Porcine collagen (absorbable)
PelviSoft™ Biomesh	Porcine collagen (absorbable)
Pelvilace®, Pelvilace® TO	Porcine collagen (absorbable)
Synthetic mesh	
Parietex™ Ugytex™ / Kit	Polypropylene textile (permanent) and porcine collagen film
Pelvitex™ / Avaulta™ System	Polypropylene textile (permanent) and porcine collagen film (absorbable)
Parietene Duo™/Quadra™	Polypropylene textile (permanent)
Parietex™ ProSup™	Polyester textile (permanent)
Uretex™	Polypropylene textile (permanent)
IVS™, IVS™ Tunneler	Polypropylene textile (permanent)

7. Please can you provide sales data for each device, and if known, market share.
We consider this as no longer relevant. Surgical mesh implants identified herein are no longer manufactured.

8. Please provide details of any post-marketing vigilance studies of relevance to the Review, including 522 studies if appropriate.

No 522 study was conducted. Medtronic has conducted the following post-market clinical studies on the devices listed herein:

- A prospective observational study on the use of Uretex™ (transobturator placement) in the treatment of UI was conducted from April 2004 to December 2005. A total of 226 subjects were enrolled, among which 166 patients were followed out to twelve months. The complication rate at 12 months was 7.9% and consisted mainly of urinary tract infections. Retention, dyspareunia and other surgical complications occurred in 4.2% of women. At the 12-month visit, the overall incidence of pain was 3% and the incidence of permanent pain was 1.2%. Eight patients out of 166 patients followed-up at 12 months (4.8%) required reintervention, among which one patient was suffering from urethral erosion and two for recurrence.
- A prospective observational study on the use of Ugytex™ in the treatment of POP was conducted from March 2002 to May 2004, which involved 238 subjects. A total of 230 patients were analyzed (8 patients excluded for deviations to the protocol) with a mean postoperative follow-up of27.8 months (0.9-55.7 months). During the first 12 months of followup, the overall vaginal erosion rate was 7.8% (n=18). At the mean follow-up time of 27.8 months, the overall vaginal erosions rate was of 13.5% (n=31) and the rate of reoperation was 27.4% (n=63). De novo dyspareunia was reported in 13 patients out of the 123 women without preoperative dyspareunia (10.6%). The most frequent complication requiring reoperation was vaginal erosion due to the Ugytex™ mesh (8.7% of the total cohort and 40% of all complications, n=50).

9. Please can you supply a summary of in-vivo shrinkage data relevant to your products.

Medtronic has not conducted in vivo testing in models intended to measure material shrinkage. In vivo testing was conducted as part of the biocompatibility testing per established standards, as applicable.

10. Please could you provide a timeline outlining your understanding and recognition of risks regarding the use of synthetic polymer mesh in pelvic surgery. This may include: initial recognition of the risk, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients.

Medtronic conducts risk assessment for all its devices per applicable standards, which includes initial hazards evaluation and periodic updates. Medtronic also maintains a post market vigilance program for all its devices. Clinical evaluations documented in the form of a critical reviews of published literature and available clinical data on the products also provide updated information regarding the risks of the devices, in accordance with the European directive 93/42/EEC and applicable European MEDDEV guidelines.

Medtronic monitors all communications/recommendations published by Competent Authorities and Sanitary Agencies, including but not limited to: MHRA[4], FDA[567], the Dutch Healthcare Inspectorate[8], TGA[9], NICE[10], HAS[11] and SCENIHR[12]. Medtronic has also maintained continued communication when prompted by Competent Authorities and Sanitary Agencies.

11. Please can you provide details of your relevant policies and protocols, if any, for ensuring that information relevant to patient safety, and learning from adverse events is disseminated.

Potential adverse events that may be associated with the use of the device and/or the surgery are disclosed in the instructions for use provided with each device. Safety information relevant to the use of the devices are also provided in the form of warnings/precautions in the instructions for use supplied with each device and intended to be read by the surgeons using the device. The procedures in place for the management of labeling materials established by the manufacturing facility ensure the systematic provision of such information to the surgeon who uses the device.

12. Please describe the steps you take in your post-marketing vigilance, and any policies you've introduced to recognise and respond to events proactively.

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[4] MHRA. Responsibilities of the parties involved in the manufacture, regulation and surgical provision of vaginal meshes. Information published on website. 2013.
[5] FDA. FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence. October 2008.
[6] FDA. Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse. July 2011.
[7] Obstetrics and Gynecology Devices Panel Meeting, September 8-9, 2011. Meeting materials.
[8] Dutch Healthcare Inspectorate assessment report. Transvaginal Mesh:Serious Complications Demand Cautious Use. July 2013.
[9] TGA. TGA Public Communication. Urogynaecological surgical mesh implants - statement provided to the Report (ABC) by the TGA. October 15, 2012.
[10] National Institute for Health and Clinical Excellence (NICE) Review. Xueli Jia, Cathryn Glazener, Graham Mowatt, Graeme MacLennan, Cynthia Fraser, Jennifer Burr. Systematic review of the efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse. October 2007.
[11] Haute Autorité de Santé (HAS). Evaluation des implants de renfort pour le traitement de l'incontinence urinaire d'effort féminine et du prolapsus des organes pelviens de la femme. Révision de la description générique de la Liste des Produits et Prestations Remboursables : « Implant pour colposuspension, peri ou sous uretrocervical ». July 2007.
[12] Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Final Opinion on The safety of surgical meshes used in urogynecological surgery. December 2015.

We consider this as no longer relevant. Surgical mesh implants identified herein are no longer manufactured.

13. Please can you supply a summary of adverse event reports, with dates of receipt but fully anonymised, related to use of synthetic mesh in pelvic surgery.

Our current complaint data is limited to the past five years. Please refer to the attached list of adverse event reports with dates of receipt related to the use of synthetic mesh in pelvic surgery between October 2013 and September 2018.

14. In your view, where within the healthcare system does your corporate responsibility lay for disseminating and responding to adverse event reporting begin and end?

Medtronic maintains a system to evaluate all adverse event reports that it receives, follow up with physicians or patients for further information, report to relevant government authorities, conduct internal analyses including trending and risk assessments, and take appropriate action either on its own or in conjunction with regulators to inform patients or health care providers about potential risks that may have been identified from adverse events.

15. Who has the final say on what should be included on the data sheets and patient information leaflets? If you have exceeded the minimum requirements specified by the regulator please provide details.

Information related to the safe use of the devices are provided in the instructions for use provided with each device. These include potential adverse events that may be associated with the use of the device and/or the surgery. Safety information relevant to the use of the devices are also provided in the form of warnings/precautions in the instructions for use supplied with each device and intended to be read by the surgeons using the device.

16. Please can you describe the elements of your corporate social responsibility policy which relate to the availability of products, and the risk-benefit analysis for products that you manufacture?

Medtronic's corporate social responsibility statement articulates our approach to quality as follows:

• Approaching quality holistically – not just with products, but in everything we do (see visual below)

• Having comprehensive, closed-loop processes across the entire product lifecycle

• Being proactive – to prevent and uncover issues early

• Being collaborative – working with physicians who are closest to our products and processes

• Being transparent – sharing our expectations and performance and with all our stakeholders, and raising awareness of potential issues early

More detail regarding this policy can be found on our website through the following link:

http://www.medtronic.com/us-en/about/corporate-social-responsibility/medical-device-quality.html

Medtronic has numerous policies and procedures to implement these principles on a more specific basis across the company.

17. If applicable, please can you provide a brief summary of litigation and/or settlements relevant to your product(s), both within the UK and worldwide?

The Company is currently involved in litigation in various state and federal courts against manufacturers of pelvic mesh products alleging personal injuries resulting from the implantation of those products. Two subsidiaries of Covidien supplied pelvic mesh products to one of the manufacturers, C.R. Bard (Bard), named in the litigation. The litigation includes a federal multi-district litigation in the U.S. District Court for the Northern District of West Virginia and cases in various state courts and jurisdictions outside the U.S. Generally, complaints allege design and manufacturing claims, failure to warn, breach of warranty, fraud, violations of state consumer protection laws and loss of consortium claims. In fiscal year 2016, Bard paid the Company $121 million towards the settlement of 11,000 of these claims. In May 2017, the agreement with Bard was amended to extend the terms to apply to up to an additional 5,000 claims. That agreement does not resolve the dispute between the Company and Bard with respect to claims that do not settle, if any. As part of the agreement, the Company and Bard agreed to dismiss without prejudice their pending litigation with respect to Bard's obligation to defend and indemnify the Company. The Company estimates law firms representing approximately 15,800 claimants have asserted or may assert claims involving products manufactured by Covidien's subsidiaries. As of June 1, 2018, the Company had reached agreements to settle approximately 14,400 of these claims.

18. Do you contribute to an administrative (non-litigative) redress scheme anywhere in the world, such as the Nordic pharmaceutical insurance schemes? If so, where, and what are the terms of the contribution? What is your evaluation of the scheme?

We are not aware of any such redress scheme.

Please let us know if you have any further questions.

Kind Regards,

Victor Carbone

Post Market Vigilance Senior Analyst
Medtronic

Attachment: Adverse Event Reports – 5 Year Data

Original provided in spreadsheet format

Year of Report	Month of Report	Surgery Type	Number of Adverse Event Reports
2013	**Oct**	PELVIC ORGAN PROLAPSE	25
		STRESS UI /PELVIC ORGAN PROLAPSE	128
		STRESS URINARY INCONTINENCE	95
		UROGYNECOLOGICAL	194
	Nov	PELVIC ORGAN PROLAPSE	14
		STRESS UI /PELVIC ORGAN PROLAPSE	53
		STRESS URINARY INCONTINENCE	16
		UROGYNECOLOGICAL	44
	Dec	PELVIC ORGAN PROLAPSE	12
		STRESS UI /PELVIC ORGAN PROLAPSE	40
		STRESS URINARY INCONTINENCE	17
		UROGYNECOLOGICAL	43
2014	**Jan**	PELVIC ORGAN PROLAPSE	23
		STRESS UI /PELVIC ORGAN PROLAPSE	34
		STRESS URINARY INCONTINENCE	17
		UROGYNECOLOGICAL	20
	Feb	INGUENAL HERNIA REPAIR	1
		PELVIC ORGAN PROLAPSE	12
		STRESS UI /PELVIC ORGAN PROLAPSE	49
		STRESS URINARY INCONTINENCE	14
		UROGYNECOLOGICAL	36
	Mar	GYNECOLOGY	1
		PELVIC ORGAN PROLAPSE	12
		STRESS UI /PELVIC ORGAN PROLAPSE	55
		STRESS URINARY INCONTINENCE	32
		UROGYNECOLOGICAL	32
	Apr	PELVIC ORGAN PROLAPSE	14
		STRESS UI /PELVIC ORGAN PROLAPSE	47
		STRESS URINARY INCONTINENCE	25
		UROGYNECOLOGICAL	26
	May	PELVIC ORGAN PROLAPSE	9
		STRESS UI /PELVIC ORGAN PROLAPSE	106
		STRESS URINARY INCONTINENCE	31
		UROGYNECOLOGICAL	62
	Jun	PELVIC ORGAN PROLAPSE	5
		STRESS UI /PELVIC ORGAN PROLAPSE	50
		STRESS URINARY INCONTINENCE	26
		UROGYNECOLOGICAL	33
	Jul	PELVIC ORGAN PROLAPSE	24
		STRESS UI /PELVIC ORGAN PROLAPSE	116

Year of Report	Month of Report	Surgery Type	Number of Adverse Event Reports
		STRESS URINARY INCONTINENCE	92
		UROGYNECOLOGICAL	75
		VENTRAL HERNIA REPAIR	2
	Aug	INGUENAL HERNIA REPAIR	1
		PELVIC ORGAN PROLAPSE	20
		STRESS UI /PELVIC ORGAN PROLAPSE	57
		STRESS URINARY INCONTINENCE	49
		UROGYNECOLOGICAL	146
	Sep	INGUENAL HERNIA REPAIR	11
		PELVIC ORGAN PROLAPSE	30
		STRESS UI /PELVIC ORGAN PROLAPSE	67
		STRESS URINARY INCONTINENCE	50
		UROGYNECOLOGICAL	82
	Oct	PELVIC ORGAN PROLAPSE	26
		RECTOPEXY	1
		STRESS UI /PELVIC ORGAN PROLAPSE	139
		STRESS URINARY INCONTINENCE	91
		UROGYNECOLOGICAL	144
	Nov	PELVIC ORGAN PROLAPSE	8
		RECTOPEXY	1
		STRESS UI /PELVIC ORGAN PROLAPSE	25
		STRESS URINARY INCONTINENCE	23
		UROGYNECOLOGICAL	42
	Dec	PELVIC ORGAN PROLAPSE	6
		STRESS UI /PELVIC ORGAN PROLAPSE	23
		STRESS URINARY INCONTINENCE	11
		UROGYNECOLOGICAL	13
2015	**Jan**	INGUENAL HERNIA REPAIR	1
		PELVIC ORGAN PROLAPSE	5
		STRESS UI /PELVIC ORGAN PROLAPSE	12
		STRESS URINARY INCONTINENCE	15
		UROGYNECOLOGICAL	21
	Feb	GYNECOLOGY	1
		PELVIC ORGAN PROLAPSE	3
		STRESS UI /PELVIC ORGAN PROLAPSE	15
		STRESS URINARY INCONTINENCE	6
		UROGYNECOLOGICAL	9
	Mar	PELVIC ORGAN PROLAPSE	4
		STRESS UI /PELVIC ORGAN PROLAPSE	20
		STRESS URINARY INCONTINENCE	10
		UROGYNECOLOGICAL	11
	Apr	PELVIC ORGAN PROLAPSE	13
		STRESS UI /PELVIC ORGAN PROLAPSE	57

Year of Report	Month of Report	Surgery Type	Number of Adverse Event Reports
		STRESS URINARY INCONTINENCE	20
		UROGYNECOLOGICAL	23
	May	INGUENAL HERNIA REPAIR	1
		PELVIC ORGAN PROLAPSE	18
		STRESS UI /PELVIC ORGAN PROLAPSE	42
		STRESS URINARY INCONTINENCE	27
		UROGYNECOLOGICAL	18
	Jun	INGUENAL HERNIA REPAIR	1
		PELVIC ORGAN PROLAPSE	33
		SALPINGECTOMY	1
		STRESS UI /PELVIC ORGAN PROLAPSE	99
		STRESS URINARY INCONTINENCE	72
		UROGYNECOLOGICAL	32
	Jul	PELVIC ORGAN PROLAPSE	29
		STRESS UI /PELVIC ORGAN PROLAPSE	105
		STRESS URINARY INCONTINENCE	49
		UROGYNECOLOGICAL	26
	Aug	PELVIC ORGAN PROLAPSE	11
		STRESS UI /PELVIC ORGAN PROLAPSE	41
		STRESS URINARY INCONTINENCE	29
		UROGYNECOLOGICAL	14
		VENTRAL HERNIA REPAIR	1
	Sep	PELVIC ORGAN PROLAPSE	5
		STRESS UI /PELVIC ORGAN PROLAPSE	19
		STRESS URINARY INCONTINENCE	10
		UROGYNECOLOGICAL	14
		VENTRAL HERNIA REPAIR	1
	Oct	PELVIC ORGAN PROLAPSE	5
		STRESS UI /PELVIC ORGAN PROLAPSE	10
		STRESS URINARY INCONTINENCE	7
		UROGYNECOLOGICAL	18
	Nov	PELVIC ORGAN PROLAPSE	1
		STRESS UI /PELVIC ORGAN PROLAPSE	10
		STRESS URINARY INCONTINENCE	9
		UROGYNECOLOGICAL	18
	Dec	PELVIC ORGAN PROLAPSE	7
		STRESS UI /PELVIC ORGAN PROLAPSE	15
		STRESS URINARY INCONTINENCE	16
		UROGYNECOLOGICAL	19
2016	**Jan**	PELVIC ORGAN PROLAPSE	9
		STRESS UI /PELVIC ORGAN PROLAPSE	16
		STRESS URINARY INCONTINENCE	15
		UROGYNECOLOGICAL	11

Year of Report	Month of Report	Surgery Type	Number of Adverse Event Reports
	Feb	PELVIC ORGAN PROLAPSE	5
		STRESS UI /PELVIC ORGAN PROLAPSE	15
		STRESS URINARY INCONTINENCE	12
		UROGYNECOLOGICAL	17
		UROLOGICAL	1
		VENTRAL HERNIA REPAIR	1
	Mar	PELVIC ORGAN PROLAPSE	41
		STRESS UI /PELVIC ORGAN PROLAPSE	45
		STRESS URINARY INCONTINENCE	96
		UROGYNECOLOGICAL	11
		VENTRAL HERNIA REPAIR	2
	Apr	PELVIC ORGAN PROLAPSE	22
		RECTOPEXY	1
		STRESS UI /PELVIC ORGAN PROLAPSE	24
		STRESS URINARY INCONTINENCE	50
		UROGYNECOLOGICAL	13
	May	PELVIC ORGAN PROLAPSE	19
		STRESS UI /PELVIC ORGAN PROLAPSE	31
		STRESS URINARY INCONTINENCE	22
		UROGYNECOLOGICAL	11
	Jun	PELVIC ORGAN PROLAPSE	16
		STRESS UI /PELVIC ORGAN PROLAPSE	45
		STRESS URINARY INCONTINENCE	25
		UROGYNECOLOGICAL	4
	Jul	PELVIC ORGAN PROLAPSE	16
		STRESS UI /PELVIC ORGAN PROLAPSE	37
		STRESS URINARY INCONTINENCE	38
		UROGYNECOLOGICAL	6
	Aug	PELVIC ORGAN PROLAPSE	9
		STRESS UI /PELVIC ORGAN PROLAPSE	43
		STRESS URINARY INCONTINENCE	23
		UROGYNECOLOGICAL	9
	Sep	PELVIC ORGAN PROLAPSE	19
		STRESS UI /PELVIC ORGAN PROLAPSE	53
		STRESS URINARY INCONTINENCE	41
		UROGYNECOLOGICAL	11
		VENTRAL HERNIA REPAIR	1
	Oct	PELVIC ORGAN PROLAPSE	33
		STRESS UI /PELVIC ORGAN PROLAPSE	94
		STRESS URINARY INCONTINENCE	105
		UROGYNECOLOGICAL	48
	Nov	PELVIC ORGAN PROLAPSE	31
		STRESS UI /PELVIC ORGAN PROLAPSE	96

Year of Report	Month of Report	Surgery Type	Number of Adverse Event Reports
		STRESS URINARY INCONTINENCE	78
		UROGYNECOLOGICAL	63
		UROLOGICAL	4
	Dec	INGUENAL HERNIA REPAIR	2
		PELVIC ORGAN PROLAPSE	6
		STRESS UI /PELVIC ORGAN PROLAPSE	62
		STRESS URINARY INCONTINENCE	39
		UROGYNECOLOGICAL	41
2017	**Jan**	PELVIC ORGAN PROLAPSE	9
		STRESS UI /PELVIC ORGAN PROLAPSE	36
		STRESS URINARY INCONTINENCE	22
		UROGYNECOLOGICAL	11
		VENTRAL HERNIA REPAIR	1
	Feb	INGUINAL HERNIA REPAIR	1
		PELVIC ORGAN PROLAPSE	19
		STRESS UI /PELVIC ORGAN PROLAPSE	97
		STRESS URINARY INCONTINENCE	54
		UROGYNECOLOGICAL	5
	Mar	GYNECOLOGY	1
		PELVIC ORGAN PROLAPSE	43
		STRESS UI /PELVIC ORGAN PROLAPSE	130
		STRESS URINARY INCONTINENCE	106
		UROGYNECOLOGICAL	13
	Apr	PELVIC ORGAN PROLAPSE	21
		STRESS UI /PELVIC ORGAN PROLAPSE	39
		STRESS URINARY INCONTINENCE	33
		UROGYNECOLOGICAL	28
		VENTRAL HERNIA REPAIR	2
	May	INGUENAL HERNIA REPAIR	1
		INGUINAL HERNIA REPAIR	2
		PELVIC ORGAN PROLAPSE	6
		STRESS UI /PELVIC ORGAN PROLAPSE	9
		STRESS URINARY INCONTINENCE	7
		UROGYNECOLOGICAL	3
		VENTRAL HERNIA REPAIR	1
	Jun	PELVIC ORGAN PROLAPSE	1
		STRESS UI /PELVIC ORGAN PROLAPSE	1
		UROGYNECOLOGICAL	4
	Jul	INGUINAL HERNIA REPAIR	1
		PELVIC ORGAN PROLAPSE	2
		STRESS URINARY INCONTINENCE	2
		UROGYNECOLOGICAL	3
	Aug	INGUINAL HERNIA REPAIR	1

Year of Report	Month of Report	Surgery Type	Number of Adverse Event Reports
		PELVIC ORGAN PROLAPSE	3
		STRESS UI /PELVIC ORGAN PROLAPSE	3
		VENTRAL HERNIA REPAIR	1
	Sep	INGUINAL HERNIA REPAIR	23
		PELVIC ORGAN PROLAPSE	3
		STRESS UI /PELVIC ORGAN PROLAPSE	12
		STRESS URINARY INCONTINENCE	3
		UROGYNECOLOGICAL	2
		VENTRAL HERNIA REPAIR	19
	Oct	INGUINAL HERNIA REPAIR	19
		PELVIC ORGAN PROLAPSE	4
		STRESS UI /PELVIC ORGAN PROLAPSE	7
		STRESS URINARY INCONTINENCE	8
		UROGYNECOLOGICAL	8
		UROLOGICAL	1
		VENTRAL HERNIA REPAIR	51
	Nov	INGUINAL HERNIA REPAIR	38
		PELVIC ORGAN PROLAPSE	5
		STRESS UI /PELVIC ORGAN PROLAPSE	39
		STRESS URINARY INCONTINENCE	16
		UROGYNECOLOGICAL	4
		VENTRAL HERNIA REPAIR	68
	Dec	INGUENAL HERNIA REPAIR	2
		INGUINAL HERNIA REPAIR	18
		PELVIC ORGAN PROLAPSE	8
		RECTOPEXY	2
		STRESS UI /PELVIC ORGAN PROLAPSE	38
		STRESS URINARY INCONTINENCE	9
		UROGYNECOLOGICAL	1
		VENTRAL HERNIA REPAIR	55
2018	**Jan**	INGUINAL HERNIA REPAIR	33
		PELVIC ORGAN PROLAPSE	3
		STRESS UI /PELVIC ORGAN PROLAPSE	3
		STRESS URINARY INCONTINENCE	4
		UROGYNECOLOGICAL	4
		VENTRAL HERNIA REPAIR	47
	Feb	INGUENAL HERNIA REPAIR	1
		INGUINAL HERNIA REPAIR	21
		PELVIC ORGAN PROLAPSE	1
		STRESS UI /PELVIC ORGAN PROLAPSE	3
		UROGYNECOLOGICAL	1
		VENTRAL HERNIA REPAIR	37
	Mar	INGUINAL HERNIA REPAIR	28

Year of Report	Month of Report	Surgery Type	Number of Adverse Event Reports
		PELVIC ORGAN PROLAPSE	1
		STRESS UI /PELVIC ORGAN PROLAPSE	4
		UROGYNECOLOGICAL	8
		VENTRAL HERNIA REPAIR	39
	Apr	INGUINAL HERNIA REPAIR	29
		PELVIC ORGAN PROLAPSE	3
		STRESS UI /PELVIC ORGAN PROLAPSE	1
		STRESS URINARY INCONTINENCE	2
		UROGYNECOLOGICAL	5
		VENTRAL HERNIA REPAIR	78
	May	PELVIC ORGAN PROLAPSE	4
		STRESS UI /PELVIC ORGAN PROLAPSE	1
		STRESS URINARY INCONTINENCE	9
		UROGYNECOLOGICAL	9
		VENTRAL HERNIA REPAIR	7
	Jun	INGUENAL HERNIA REPAIR	2
		PELVIC ORGAN PROLAPSE	5
		STRESS UI /PELVIC ORGAN PROLAPSE	12
		STRESS URINARY INCONTINENCE	1
		UROGYNECOLOGICAL	2
		UROLOGICAL	3
		VAGINAL HYSTERECTOMY	1
		VENTRAL HERNIA REPAIR	11
	Jul	PELVIC ORGAN PROLAPSE	3
		RECTOPEXY	2
		STRESS UI /PELVIC ORGAN PROLAPSE	1
		STRESS URINARY INCONTINENCE	1
		UROGYNECOLOGICAL	5
		VENTRAL HERNIA REPAIR	13
	Aug	INGUINAL HERNIA REPAIR	17
		PELVIC ORGAN PROLAPSE	1
		STRESS UI /PELVIC ORGAN PROLAPSE	5
		STRESS URINARY INCONTINENCE	5
		UROGYNECOLOGICAL	15
		VENTRAL HERNIA REPAIR	31
	Sep	INGUINAL HERNIA REPAIR	8
		UROGYNECOLOGICAL	2
		VENTRAL HERNIA REPAIR	18