WOMED LEAF®
English

Access online information : this video contains instructions for inserting the Womed Leaf® device, please watch it before using the device.

Caution
Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner.

Product information
Intrauterine adhesions (IUAs) are fibrous strings that depending on their extent and severity can obliterate the uterine cavity. Trauma to the endometrium may lead to formation of IUAs, which can be a major long-term complication of hysteroscopic surgery in women of reproductive age. Symptomatic IUAs can be associated with poor reproductive outcomes[1]. Keeping adjacent wound surfaces mechanically separated after the trauma for a sufficient period of time using a biodegradable barrier may help reduce the reoccurrence and severity of adhesion formation[1,2].

The Womed Leaf® Resorbable Adhesion Barrier is a sterile, single use, degradable film of poly(D,L-lactide) (PLA) and poly(ethylene oxide) (PEO) obtained by polymerization of PEO and D,L-lactide. When PEO is polymerized with hydrophobic PLA, it forms a film that swells and expands in contact with water to form a degradable mechanical barrier. It is fragmented by solubilization and hydrolytic degradation and is self-discharged through the cervix and the vagina within 8 weeks.

Womed Leaf® is intended to be used by healthcare professionals trained in obstetrics and gynecology.

Indications for use
The Womed Leaf® Resorbable Adhesion Barrier is intended to reduce the reoccurrence and severity of post-surgical adhesion formation inside the uterus. It is indicated for adult women undergoing hysteroscopic surgery for symptomatic moderate to severe intrauterine adhesions.

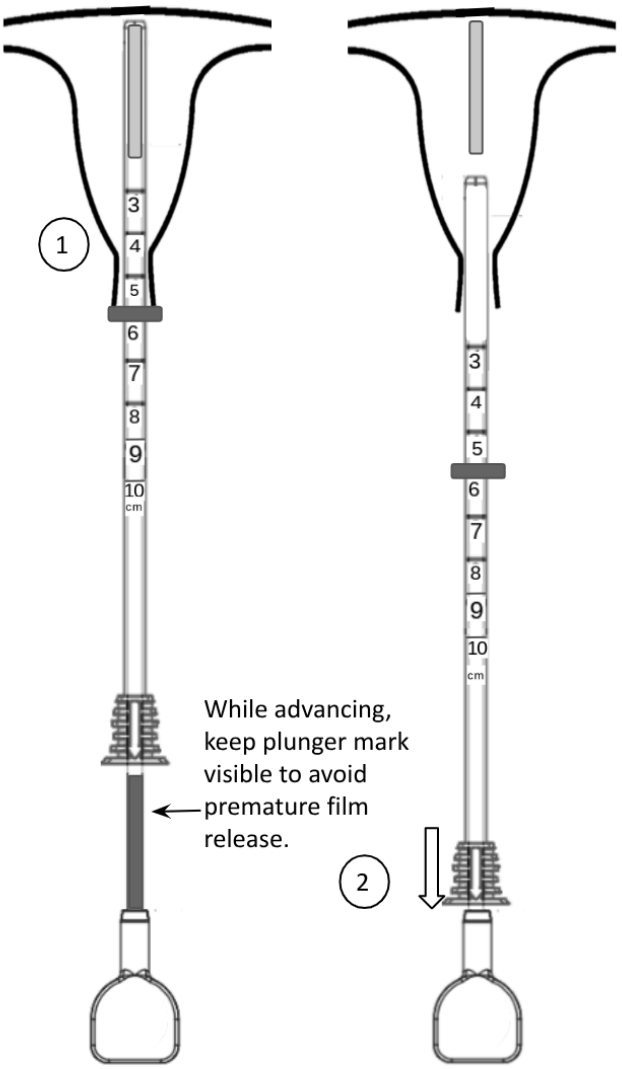
Warnings
-The Womed Leaf® device must be used according to the instructions for use. Read instructions prior to use. Failure to follow the insertion instructions may result in an incorrect positioning of the Womed Leaf® in the endometrial cavity and premature discharge.
-The Womed Leaf® device is designed and intended for single use only. Do not re-use, or re-sterilize. Reuse of the device may lead to infection leading to endometritis, salpingitis, or pelvic peritonitis.
- In case of suspicion of thin uterine wall, extra care should be taken due to the higher perforation risks.

- Adverse effects may include allergic reaction, including pruritus and vulvovaginal pruritus, infection (rash, fever), persistent pelvic pain, urethral pain or bleeding.
- Womed Leaf® should not be used in pregnancy.
- Do not use the product if the temperature indicator on the box is black or if the protective pouch is damaged or unintentionally opened before use as sterility may be compromised.

Precautions
- The safety and effectiveness of Womed Leaf® has not been established in patients with an abnormal uterine cavity (i.e., unicornis, bicornis, septate, duplex).
- The safety and effectiveness of Womed Leaf® has not been established in patients with a history of endometrial ablation.
- The safety and effectiveness of Womed Leaf® has not been established in patients with a uterine length >10 cm.
- The safety and effectiveness of Womed Leaf® has not been established following hysteroscopic procedures other than adhesiolysis of moderate to severe adhesions.
-Uterine film placement can be verified post-procedure by ultrasound imaging.
-During inserter preparation and insertion, keep plunger mark visible to avoid premature film release.
-Patients should be informed to avoid pregnancy during the first complete menstrual cycle subsequent to the treatment with Womed Leaf®.

Contraindications
Known hypersensitivity to Womed Leaf® or any of its components.
The device must not be used in patients with infection or contamination of the procedure site.

Instructions for use
Womed Leaf® is provided in a sterile single-use inserter. It has been sterilized by beta irradiation. Manipulation of the Womed Leaf® should be performed with sterile gloves. At least 3 ml of fluid should be present in the uterus prior to device insertion.
1. Measure the length of the uterine cavity with a uterine sound (not supplied by Womed®) and select the appropriate size according to the uterine length (see table 1).
2. Take the product out of refrigeration and check that the temperature indicator on the packaging box has not turned black. If it has, the product should not be used and should be discarded.
3. Open the sterile pouch adopting standard aseptic techniques used in the surgical theater.
4. Position the uterine length ring accordingly on the inserter. Advance the plunger until the outer sheath is in contact with the plunger mark.
5. Carefully introduce the inserter through the cervix. The inserter should be advanced in the proper plane: the arrow and the scale pointing up. While advancing, keep plunger mark visible to avoid premature film release.
6. When the inserter is in the desired position, release the uterine film by completely retracting the outer sheath using the arrow handle up to a full stop while holding the plunger steady with the other hand.
7. Withdraw the inserter by pulling both parts: the polymer film is now delivered in the uterus.
Womed Leaf® remains in the uterus cavity then it is fragmented and evacuated through the cervix within 8 weeks. No procedure is required to remove it. The inserter can be discarded using standard hospital procedures.



Scheme legend
① Advance the inserter until the uterine length ring is in contact with the cervix
② Retract the outer sheath completely to release the uterine film while holding the plunger steady.

Table 1: Product model and corresponding uterine length

Model	Size	Uterine length
LEAF-S	SMALL	< 5 cm
LEAF-M	MEDIUM	5 - 7 cm
LEAF-L	LARGE	7 - 10 cm

At the length border (5 or 7 cm), select the larger size

Clinical studies

Pilot study

Note: The pilot study population is different from the approved study population. Pilot study information is provided to communicate safety and effectiveness outcomes that may be relevant to the approved patient population for the Womed Leaf®. The safety and effectiveness of Womed Leaf® has not been established in the pilot study population.

The safety and the potential efficacy of Womed Leaf® was evaluated in a prospective, multi-center, single arm clinical study (the PREG1 clinical trial), after transcervical resection of myoma (TCRM). Patients enrolled in this study had one or more myoma(s) with one myoma larger than 10mm, qualified for hysteroscopic myomectomy, were more than 40 years in age and had no childbearing wish, or history of permanent sterilization. All subjects were contacted at 30 days post procedure to assess their clinical status and adverse events, then a second look diagnostic hysteroscopy procedure was performed between 4 to 8 weeks to assess the uterine cavity and the presence of intrauterine adhesions. The co-primary endpoints for the study were the number and type of device-related adverse events (AEs) up to 30 days (safety endpoint), and the freedom from IUAs at second look hysteroscopy between 4 and 8 weeks, and the evaluation of severity according to American Fertility Society (AFS) and European Society of Gynecological Endoscopy (ESGE) classifications systems of adhesions (efficacy endpoints). Secondary safety and effectiveness endpoints were also evaluated (i.e., the performance of the Womed Leaf® inserter defined as the insertion into the uterus with the loaded film and the release of the Womed Leaf® uterine film in the uterus defined as empty inserter after withdrawal, the device manipulation duration, the menstrual periods following index procedure and before SLH according to Higham score, the subject estimation of film discharge timing and duration as well as the discomfort assessment and qualitative impression were recorded at SLH, and the presence of Womed Leaf® film remnants in the uterus at SLH).

23 subjects were enrolled in 6 investigational sites in the European Union and completed the study follow-up visits. The subjects were 47 years old on average; a mean of 1.3 myoma was resected with a mean diameter of 2.7 cm and 82% were of type 1 or 2.

SAFETY RESULTS
There were three adverse events (blood loss in the abdominal cavity due to concomitant laparoscopy, hematoma in the myoma resection area, kidney colic). None were designated to be device related.

EFFICACY RESULTS
Out of the 23 patients, 20 were free of adhesion at second look hysteroscopy (87%); out of the three reported adhesions, none were classified as severe. According to the AFS, two were classified as mild and one was classified as moderate. According to the ESGE, one was classified as mild and two were classified as moderate. The performance of the Womed Leaf® inserter was 100% successful from the first attempt with a device manipulation duration from insertion to withdrawal estimated at less than 2 minutes. Thirteen women reported menstruation between myomectomy and second look hysteroscopy with a Higham score recorded of 247 +/- 222 in 8 women. Thirteen women remembered observing the film discharge, the others did not notice the film discharge. The film discharge duration was estimated at between a few hours and more than a day, and the median discomfort was 1 (min=1, max=7) on a scale from 1 (no pain) to 10 (very painful). There were no film residues and there was no report of abnormal endometrium at the second look hysteroscopy.

Pivotal study
The safety and effectiveness of Womed Leaf® have been evaluated in a multicenter, international (outside the United States), double-blind, randomized, controlled superiority pivotal stratified by IUA severity and site (the PREG2 trial), involving 163 women with moderate or severe IUAs, where hysteroscopic adhesiolysis followed by insertion of Womed Leaf® was compared to adhesiolysis alone. Subjects were contacted 2 weeks post procedure to assess their clinical status and adverse

events.* A follow-up diagnostic hysteroscopy was performed 6 weeks (+/- 2 weeks) after surgery to determine the presence and severity of recurring IUAs according to the American Fertility Society (AFS) classification systems of adhesions.

Table 2: Subject demographics and baseline characteristics

	Control (n=85)	**Womed Leaf® (n=75)**
Age, mean ± SD, year	35.9 ± 5.1	35 ± 5.2
BMI, mean ± SD, (kg/m²)	23.8 ± 4.8	24.1 ± 4.3
Ethnicity		
Hispanic or Latino**	5 (5.9%)	4 (5.3%)
Not Hispanic or Latino	80 (94.1%)	71 (94.7%)
Race		
Asian	15 (17.6%)	13 (17.3%)
Black or African	18 (21.2%)	15 (20.0%)
White (from Europe, the Middle East, or North Africa)	52 (61.2%)	47 (62.7%)
Clinical manifestations* **		
Dysmenorrhea	23 (27.1%)	18 (24.0%)
Noncyclic pelvic pain	8 (9.4%)	1 (1.3%)
Infertility	57 (67.1%)	49 (65.3%)
Abnormal placentation	5 (5.9%)	2 (2.7%)
Recurrent pregnancy loss	10 (11.8%)	9 (12.0%)
Amenorrhea/hypomenorrhea/oligomenorrhea	11 (12.9%)	13 (17.3%)
Other	5 (5.9%)	2 (2.7%)
Menstrual pattern		
Absent (amenorrhea)	31 (36.5%)	24 (32.0%)
Light (hypomenorrhea)	35 (41.2%)	30 (40.0%)
Normal	19 (22.4%)	21 (28.0%)
Surgical history on uterus (mITT set)		
Number of previous adhesiolysis		
None	44 (51.8%)	40 (53.3%)
1	18 (21.2%)	15 (20.0%)
2	11 (12.9%)	9 (12.0%)
3	6 (7.1%)	7 (9.3%)
>3	6 (7.1%)	4 (5.3%)
Number of previous operative hysteroscopies		
None	32 (37.6%)	33 (44.0%)
1	26 (30.6%)	17 (22.7%)
2	9 (10.6%)	12 (16.0%)
3	8 (9.4%)	7 (9.3%)
>3	10 (11.8%)	6 (8.0%)
History of uterine artery embolization	6 (7.1%)	11 (14.7%)

	Control (n=85)	Womed Leaf® (n=75)
Cause of IUA formation* **		
Dilatation and curettage for miscarriage or termination of pregnancy	48 (56.5%)	39 (52.0%)
Postpartum dilatation and curettage (retained product of conception)	18 (21.2%)	13 (17.3%)
Uterine embolization	5 (5.9%)	10 (13.3%)
Hysteroscopic myomectomy	8 (9.4%)	3 (4.0%)
Hysteroscopic polypectomy	2 (2.4%)	2 (2.7%)
Hysteroscopic uterine septum (resection/metroplasty)	1 (1.2%)	0 (0.0%)
Laparoscopic myomectomy	3 (3.5%)	1 (1.3%)
Abdominal myomectomy	5 (5.9%)	6 (8.0%)
Cesarean section	9 (10.6%)	13 (17.3%)
Other	11 (12.9%)	10 (13.3%)
Obstetrical history		
Parity		
None	26 (30.6%)	32 (42.7%)
1	36 (42.4%)	33 (44.0%)
2	15 (17.6%)	6 (8.0%)
3	6 (7.1%)	3 (4.0%)
>3	2 (2.4%)	1 (1.3%)
Gravidity		
None	9 (10.6%)	8 (10.7%)
1	26 (30.6%)	31 (41.3%)
2	18 (21.2%)	17 (22.7%)
3	15 (17.6%)	8 (10.7%)
4	9 (10.6%)	5 (6.7%)
>4	8 (9.4%)	6 (8.0%)
Number of previous dilation and curettage procedures		
None	28 (32.9%)	27 (36.0%)
1	36 (42.4%)	24 (32.0%)
2	16 (18.8%)	15 (20.0%)
3	3 (3.5%)	4 (5.3%)
>3	2 (2.4%)	5 (6.7%)
Number of previous spontaneous miscarriage		
None	42 (49.4%)	46 (61.3%)
1	22 (25.9%)	14 (18.7%)
2	12 (14.1%)	8 (10.7%)
3	8 (9.4%)	0 (0.0%)
4	0 (0.0%)	3 (4.0%)
>4	1 (1.2%)	4 (5.3%)
Number of previous pregnancy termination		
None	56 (65.9%)	52 (69.3%)
1	22 (25.9%)	14 (18.7%)
2	3 (3.5%)	6 (8.0%)
3	3 (3.5%)	2 (2.7%)
4	1 (1.2%)	1 (1.3%)
IUA severity BEFORE adhesiolysis		
Mean ± Standard Deviation	8.2±2.0	8.2±2.2

	Control (n=85)	Womed Leaf® (n=75)
IUA severity BEFORE adhesiolysis Stage II (moderate i.e. 5⩽AFS score⩽8) Stage III (severe i.e. 9⩽AFS score⩽12)	 59 (69.4%) 26 (30.6%)	 51 (68.0%) 24 (32.0%)
Presence of IUA at the end of the surgery	15%	13%
mITT set * World Health Organization Classification ** Hispanic or Latino from Cuba, Mexico, Puerto Rico, South or Central America or other Spanish culture or origin, regardless of race *** Several possible answers		

Table 3: Patient disposition

	Overall	Control group	Womed Leaf® group
Assessed for eligibility	191		
Ineligible	28		
Enrolled	163		
Randomized (ITT set)	163	85	78
Randomized before surgery and excluded based on intraoperative exclusion criteria	3		
Included in mITT analysis	160	85	75
Discontinued follow-up	7	3	4
Reasons for discontinuation - Pregnancy before SLH - Unwilling to meet for the follow-up SLH		 1 2	 3 1
Included in the complete case analysis	153	82	71

Table 4: Inclusion and exclusion criteria

Inclusion criteria:

1. Women with symptomatic moderate or severe intrauterine adhesions according to the AFS classification, i.e AFS score ≥5, confirmed by hysteroscopy during adhesiolysis
2. Scheduled for hysteroscopic adhesiolysis
3. Age ≥ to 18
4. Subjects who are willing to provide a written informed consent.
5. Subjects who can comply with the study follow-up (and benefit from second look hysteroscopy) and other study requirements.
6. Subjects who agree to refrain from intercourse or use a reliable form of contraception to prevent unintended pregnancy until the second look hysteroscopy (SLH).
7. Subjects who agree to avoid all intrauterine devices (IUDs) until the SLH.

Exclusion criteria:

Pre-operative exclusion criteria

1. Post menopause
2. Pregnant (confirmed by a positive pregnancy test) or lactating
3. Abnormal uterine cavity according to ESHRE classification I to V such as unicornis, bicornis, septate, duplex
4. Known or suspected endometrial hyperplasia
5. History of cervical or endometrial cancer
6. Active pelvic infection or history of pelvic peritonitis
7. History of endometrial ablation
8. Known contraindication or hypersensitivity to Womed Leaf® component
9. Current participation in another clinical investigation that has not yet received the primary endpoint.
10. Any other condition that makes participation in the study contrary to the patient's best interests.

Intra-operative exclusion criteria, post adhesiolysis:

11. Perforation during adhesiolysis
12. Sounded uterine length < 5cm or > 10cm

Table 5: Number of participants per device size

Device size	Number of participants
Small	2
Medium	60
Large	13

SAFETY RESULTS

The analysis of safety was based on the safety cohort of 163 patients. No serious adverse event was reported during the 6 weeks follow-up period of the trial. The adverse events that occurred until the 6-week evaluation, reported as per protocol, are presented in Table 6. Additionally, no polymer remnant or endometrial abnormalities were reported during the trial. The patient-reported outcomes, collected at the 6-week follow-up visit are presented in Table 7.

Table 6 summary of adverse events*

	Control Group	Womed Leaf®	Relationship with the study device according to the investigator	Timeframe (after surgery)	Severity (assessed by the investigator)
Safety population	**86**	**77**			
Abdominal pain	1 (1.2%)		possibly related	10 days	Mild
Pyrexia (Fever)	1 (1.2%)		not related	9 days	Mild

Neuralgia	1 (1.2%)		not related	9 weeks	Moderate
Uterine perforation at SLH		1 (1.3%)	not related	6 weeks	Mild
Liver function test abnormal		1 (1.3%)	not related	6 weeks	Mild
Urethral pain		1 (1.3%)	possibly related	1 week	Mild
Vulvovaginal pruritus		1 (1.3%)	possibly related	10 days	Mild
Cervix disorder		1 (1.3%)	not related	At the beginning of surgery (before WL insertion)	Mild
Pruritus		1 (1.3%)	possibly related	6 days	Mild
Postoperative pain*	22 (26.8%)	12 (16.9%)	Not related	73% occurred within 6 days post surgery (n=24/33)	Median level of pain** = 4/10 in the control group vs 3/10 in the Leaf group
Discomfort related to vaginal discharge*	8 (9.8%)	7 (9.9%)	Not related	52% of vaginal discharges occurred within 6 days post surgery	Median level of discomfort** = 3/10 in the control group vs 2/10 in the Leaf group
Total number of patients with at least 1 event	31 (36.0%)	20 (26.0%)			
* in the subset of patients who reported the outcome (n=82 in the control group and 71 in the Leaf group)					
** assessed by the patient					

*Adverse events were collected at 2 weeks for 76/163 subjects (47%), as the clinical study was updated in clinical study protocol version 3.2 to add this 2-week assessment visit, and during the 6 weeks follow-up visit for all subjects.

Table 7: Patient outcomes collected by questionnaire

	Control group (n=82)	**Womed Leaf® group (n=71)**	
Presence of post-operative pain	22 (26.8%)	12 (16.9%)	
Presence of vaginal discharge	19 (23,2%)	25 (35,2%)	
Presence of discomfort related to vaginal discharge	8 (9.8%)	7 (9.9%)	

Specified patient outcomes were collected via questionnaire by the investigator at the 6-week visit but did not follow the same pathway assessment as adverse events (i.e., were not evaluated or adjudicated by the investigator).

EFFECTIVENESS RESULTS

The analysis of effectiveness was based on the 153 evaluable patients at the 6-week time point. Primary outcome and secondary effectiveness outcomes are presented in Table 8 and 9. The trial met its primary endpoint: the reduction of AFS score between baseline and second-look hysteroscopy was statistically significantly higher in the Womed Leaf® group than in the control group.

Table 8: Primary outcome collected at SLH (mITT set)

Primary outcome : Change of AFS score between pre-adhesiolysis and SLH			
	Control (n=82)	**Womed Leaf® (n=71)**	**p value**
Mean ± Standard Deviation	4.2 ± 3.2	5.2 ± 2.8	0.0153

Table 9: Secondary outcome collected at SLH (mITT set)

#	Description	Control group (n=82)	Womed Leaf® group (n=71)	p value	Odds ratio [95%CI]
1	High-responder rate	24 (29.3%)	36 (50.7%)	0.0052	2.72 [1.35; 5.45]
2	Change of "extent of cavity involved" component (according to the 10-zone diagram) between pre-adhesiolysis and SLH* (Mean ± Standard Deviation)	2.9 ± 2.4	3.6 ± 2.0	0.0209	2.08 [1.119; 3.863]
3	Change of "extent of cavity involved" component between post-adhesiolysis and SLH (Mean ± Standard Deviation)	-1.9 ± 2.4	-1.2 ± 2.1	0.0167	2.15 [1.15 ;4.02]
4	AFS score at SLH (Mean ± Standard Deviation)	4.0 ± 3.3	3.0 ± 3.2	0.0052	0.40 [0.211; 0.757]
5	"Extent of IUA" score component at SLH: ● 0 ● < 1/3 ● 1/3 - 2/3 ● > 2/3	 20 (24.4%) 48 (58.5%) 8 (9.8%) 6 (7.3%)	 29 (40.8%) 33 (46.5%) 8 (11.3%) 1 (1.4%)	0.0162	2.22 [1.16; 4.24]
6	"Type of IUA" score component at SLH: ● No IUA ● Filmy ● Filmy and Dense ● Dense	 20 (24.4%) 22 (26.8%) 11 (13.4%) 29 (35.4%)	 29 (40.8%) 16 (22.5%) 7 (9.9%) 19 (26.8%)	0.0747	1.82 [0.94; 3.52]
7	"Menstrual pattern" score component at SLH ● Normal ● Hypomenorrhea ● Amenorrhea	n=83 52 (62.7%) 17 (20.5%) 14 (16.9%)	n=71 49 (69.0%) 14 (19.7%) 8 (11.3%)	/	/

8	Patients with mild adhesions or no IUA at SLH	46 (56.1%)	46 (64.8%)	/	/
9	Freedom from IUAs	n=82 20 (24.4%)	n=71 29 (40.8%)	/	/
10	ESGE stage at second look hysteroscopy* ● Grade I ● Grade II ● Grade IIa ● Grade III ● Grade IV ● Grade Va ● Grade Vb	n=62 19 (30.6%) 18 (29.0%) 1 (1.6%) 11 (17.7%) 7 (11.3%) 2 (3.2%) 4 (6.5%)	n=42 14 (33.3%) 7 (16.7%) 0 (0.0%) 13 (31.0%) 5 (11.9%) 1 (2.4%) 2 (4.8%)	/	/
11	Change of menstrual pattern ● Worsening ● No change ● Improvement	n=83 4 (4.8%) 34 (41.0%) 45 (54.2%)	n=71 5 (7.0%) 28 (39.4%) 38 (53.5%)	/	/
12	Responder rate**	57 (69.5%)	55 (77.5%)	/	/

The parameter for the odds ratio is the randomization group with the control group as reference.
*Calculated as follows: Number of zones involved before adhesiolysis - Number of zones involved at SLH

CONCLUSION
The PREG2 randomized controlled trial demonstrated that Womed Leaf® significantly reduced the severity of intrauterine adhesion after hysteroscopic adhesiolysis compared with no prevention method and that Womed Leaf® has an acceptable safety profile.

How supplied and storage
Womed Leaf® is presented in a single sterile pouch. The pouch is opaque and the device is packed with nitrogen to control humidity.
Keep refrigerated below 8°C.

Shelf-life
The shelf-life of the Womed Leaf® device is 2 years. Use the Womed Leaf® device prior to the expiration date specified on the package.

References
1- Weyers S., Capmas P., Huberlant S., et al. Safety and Efficacy of a Novel Barrier Film to Prevent Intrauterine Adhesion Formation after Hysteroscopic Myomectomy: The PREG1 Clinical Trial. Journal of Minimally Invasive Gynecology 2021
2- Fernandez H., Miquel L., Sroussi J., et al. Effectiveness of degradable polymer film in the management of severe or moderate intrauterine adhesions (PREG-2): a randomized, double-blind, multicenter, stratified, superiority trial. Fertility and sterility Vol. 122, No. 6,2024

Symbols used in labeling

Symbol	Symbol title and description	Symbol Reference

Rx only	Caution: Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner	21 CFR 801
	Use-by date; Indicates the date after which the medical device is not to be used	ISO 15223-1:2021, 5.1.4
	Batch code; Indicates the manufacturer's batch code so that the batch or lot can be identified	ISO 15223-1:2021, 5.1.5
	Catalog number; Indicates the manufacturer's catalog number so that the medical device can be identified	ISO 15223-1:2021, 5.1.6