Baxter

Seprafilm

ADHESION BARRIER

CHEMICALLY MODIFIED SODIUM HYALURONATE/
CARBOXYMETHYLCELLULOSE
ABSORBABLE ADHESION BARRIER

SEPRAFILM® ADHESION BARRIER

DESCRIPTION
Seprafilm® Adhesion Barrier (membrane) is a sterile, bioresorbable, translucent adhesion barrier composed of two anionic polysaccharides, sodium hyaluronate (HA) and carboxymethylcellulose (CMC). Together, these biopolymers have been chemically modified with the activating agent 1-(3-dimethylaminopropyl) -3- ethyl-carbodiimide hydrochloride (EDC). Seprafilm should be stored between 36°F-86°F (2°C-30°C) until the package expiration date.

INDICATIONS
Seprafilm Adhesion Barrier is indicated for use in patients undergoing abdominal or pelvic laparotomy as an adjunct intended to reduce the incidence, extent, and severity of postoperative adhesions between the abdominal wall and the underlying viscera such as omentum, small bowel, bladder, and stomach, and between the uterus and surrounding structures such as tubes and ovaries, large bowel, and bladder.

CONTRAINDICATIONS
Seprafilm Adhesion Barrier is contraindicated in patients with a history of hypersensitivity to Seprafilm and/or to any component of Seprafilm.
Seprafilm Adhesion Barrier is contraindicated for use wrapped directly around a fresh anastomotic suture or staple line as such use increases the risk of anastomotic leak and related events (fistula, abscess, leak, sepsis, peritonitis). An increased rate of anastomotic leak was identified in a postapproval study when Seprafilm Adhesion Barrier was wrapped directly around a fresh anastomotic suture or staple line.

ACTIONS
Seprafilm Adhesion Barrier serves as a temporary bioresorbable barrier separating apposing tissue surfaces. The physical presence of the membrane separates adhesiogenic tissue while the normal tissue repair process takes place. When applied as directed, Seprafilm Adhesion Barrier can be expected to reduce adhesions within the abdominopelvic cavity. Approximately 24 to 48 hours after placement, the membrane becomes a hydrated gel that is slowly resorbed within one week. Components are excreted in less than 28 days.

WARNINGS
Seprafilm Adhesion Barrier must be used according to the instructions for use. Read instructions prior to use. Seprafilm Adhesion Barrier is supplied sterile and must not be re-sterilized. The membrane is for single use only. Every opened and unused Seprafilm pouch must be discarded. Do not use product if pouch is damaged or opened. In patients undergoing surgery for ovarian, primary peritoneal or fallopian tube malignancies, Seprafilm use has been reported as having an increased risk of intra-abdominal fluid collection and/or abscess, particularly when extensive debulking surgery was required.

The safety and effectiveness of Seprafilm Adhesion Barrier has not been evaluated in clinical studies for the following involving: Patients with frank infections in the abdominopelvic cavity, patients with abdominopelvic malignancy, device placement in locations other than directly beneath an abdominal wall incision following laparotomy, or directly on the uterus following open myomectomy (not laparoscopic), patients with ongoing local and/or systemic inflammatory cell responses, device use in the presence of other implants, e.g., surgical mesh, patients requiring re-operation within 4 weeks of Seprafilm placement – during anticipated time of peak adhesion formation as is associated with natural progression of healing.

Foreign body reactions have occurred with Seprafilm Adhesion Barrier.

PRECAUTIONS
The safety and effectiveness of Seprafilm Adhesion Barrier in combination with other adhesion prevention products and/or in other surgical procedures not within the abdominopelvic cavity have not been established in clinical studies.

The safe and effective use of Seprafilm Adhesion Barrier in pregnancy and Cesarean section has not been evaluated. No clinical studies have been conducted in pregnant women or women who have become pregnant within the first month after exposure to Seprafilm Adhesion Barrier. Therefore, this product is not recommended for use during pregnancy and avoidance of conception should be considered during the first complete menstrual cycle after use of Seprafilm Adhesion Barrier.
Seprafilm Adhesion Barrier did not promote the growth of test microorganisms within the abdominopelvic cavity in animal studies.

A mean of two of the 5" x 6" Seprafilm membranes were applied to patients in the two premarket studies. In the postmarket study, a mean of 4.4 of the 5" x 6" membranes were applied to patients.

Long-term clinical outcomes such as chronic pain and infertility have not been determined in clinical studies.

ADVERSE EVENTS
Seprafilm Adhesion Barrier has been studied in five clinical trials involving 2133 patients. Two safety pilot studies enrolled a total of 32 patients; two pivotal studies enrolled a total of 310 patients. One of the pivotal studies enrolled ulcerative colitis and familial polyposis patients undergoing colectomy followed by ileal pouch anal anastomosis with temporary ileostomy. The second pivotal study enrolled uterine myomectomy patients.

A postmarket study enrolled 1791 patients (882 Seprafilm, 909 Control) with similar baseline characteristics from the United States, Canada, and Europe who underwent intestinal resections or adhesiolysis for treatment of bowel obstruction. Although there was no difference in the overall number of patients in this postmarket study with serious adverse events, a higher incidence of anastomotic leak-related events was observed in patients who had Seprafilm wrapped around a fresh anastomotic site. These complications were not observed when Seprafilm was used throughout the abdomen, without deliberately covering the anastomosis (see Table 4). However, the placement of Seprafilm under the abdominal wall incision did not affect wound healing or surgical site infection rates. In addition, there was no statistical difference between groups in the incidence of either abdominopelvic abscess or pulmonary embolism. No foreign body reaction was detected in the 882 Seprafilm patients.

A summary of all serious adverse events occurring in the pivotal premarket trials (Tables 1 and 2) and the postmarket study (Tables 3 and 4) are provided in the tables below.

Summary of Serious Adverse Events in Clinical Trials

Table 1: Colectomy/Ileal Pouch Anal Anastomosis Patients

Event Description	Percentage of Seprafilm Membrane Patients with Event	Percentage of Control Patients with Event
Number of Colectomy/Ileal Pouch Anal Anastomosis Patients	**N=91**	**N=92**
Small bowel obstruction	9%	10%
Abscess	8%	2%
Generalized Signs and Symptoms		
Nausea/Vomiting/Diarrhea	4%	5%
Pulmonary embolus	4%	0%
Deep vein thrombosis	2%	1%
Ileus	2%	1%
Fever	2%	0%
Adrenal insufficiency	2%	0%
Sepsis	1%	1%
Myocardial infarction/Death	1%	0%
Pancreatitis	1%	0%
Mesenteric thrombus	1%	0%
Hepatotoxicity	1%	0%
Ventricular arrhythmia	1%	0%
Large blood clot/Rectum	0%	1%
Urinary retention	1%	0%
Dehydration	0%	1%
Pouchitis	1%	0%
Rectovaginal fistula	0%	1%

No statistically significant differences were detected between the Seprafilm and control groups.

Almost 90% (n=39) of all serious events reported in Seprafilm Adhesion Barrier–treated patients and nearly 81% (n=22) of those reported in control patients occurred during the trial, which required colectomy followed by ileal pouch anal anastomosis (IPAA).

Table 2: Myomectomy Patients

Event Description	Percentage of Seprafilm Membrane Patients with Event	Percentage of Control Patients with Event
Number of Myomectomy Patients	**N=59**	**N=68**
Ileus and Fever	2%*	0%
Fever-blood typing error	2%	0%
Laparoscopy converted to laparotomy	0%	1%
Intra-abdominal bleeding	0%	1%
Atelectasis and Ileus	0%	1%
Postoperative fever	0%	1%

* Associated with retained laparotomy pack.
No statistically significant differences were detected between the Seprafilm and control groups.

The frequency of serious adverse events during the uterine myomectomy study was 3% (n=2) in the Seprafilm Adhesion Barrier group and 4% (n=4) in the control group.

Table 3: 30-Day and 6-Month SAEs that Occurred in ≥1% of All Randomized Patients (N=1791) who had Either Intestinal Resections or Adhesiolysis (postmarket study)

Event Description	30-Day Seprafilm Patients (N=882 patients)	30-Day Control Patients (N=909 patients)	6-Month Seprafilm Patients (N=882 patients)	6-Month Control Patients (N=909 patients)
	n (%) Patients With Event	n (%) Patients With Event	n (%) Patients With Event	n (%) Patients With Event
Any SAE	264 (30)	237 (26)	350 (40)	324 (36)
Ileus	40 (5)	40 (4)	51 (6)	46 (5)
Intestinal obstruction[1]	38 (4)	33 (4)	65 (7)	68 (8)
Anastomotic leak	33 (4)*	16 (2)	41 (5)	28 (3)
Dehydration	26 (3)	32 (4)	44 (5)	47 (5)
Abdominopelvic abscess[2]	30 (3)	27 (3)	48 (5)	43 (5)
Peritonitis	26 (3)*	12 (1)	31 (4)	18 (2)
Postoperative wound infection[3]	30 (3)	27 (3)	37 (4)	30 (3)
Abdominal pain	18 (2)	15 (2)	28 (3)	26 (3)
Fever	15 (2)	24 (3)	22 (3)	32 (4)
Fistula[4]	16 (2)*	2 (<1)	26 (3)*	7 (1)
Vomiting	13 (2)	13 (1)	22 (3)	20 (2)
Sepsis	17 (2)	9 (1)	21 (2)	13 (1)
Wound dehiscence[5]	12 (1)	9 (1)	16 (2)	10 (1)
Gastrointestinal disorder NOS	7 (1)	8 (1)	13 (2)	13 (1)
GI hemorrhage	9 (1)	3 (<1)	13 (2)	8 (1)
Nausea	6 (1)	5 (<1)	12 (1)	11 (1)
Intra-abdominal fluid collection	9 (1)	6 (1)	11 (1)	6 (1)
Urinary tract infection	8 (1)	7 (1)	11 (1)	10 (1)
Line infection	7 (1)*	1 (<1)	10 (1)	5 (1)
Thrombophlebitis leg deep	3 (<1)	4 (<1)	9 (1)	7 (1)

* Statistically significant difference detected between the Seprafilm and control groups ($p<0.05$).
[1] Intestinal obstructions were spontaneously reported obstructions of all causes during the postoperative 30-day and 6-month period.
[2] Abdominopelvic abscess included abdominal abscess and pelvic abscess.
[3] Postoperative wound infection included postoperative wound infection and wound abscess.
[4] Fistula included fistula and intestinal fistula.
[5] Wound dehiscence included fascial wound dehiscence, superficial wound dehiscences, and wound dehiscence.

The frequency of serious adverse events between 0 and 30 days during the postmarket study was 30% (n=264) in the Seprafilm Adhesion Barrier group and 26% (n=237) in the control group. The incidence of serious adverse events at 6 months increased by the addition of approximately 10% in each group to 40% (n=350) in the Seprafilm Adhesion Barrier group and 36% (n=324) in the control group.

A retrospective analysis of anastomotic leak-related abdominal adverse events in the postmarket study is given in the tables below. This retrospective analysis compares the rates of abdominal adverse events occurring between 0 and 30 days when Seprafilm is or is not wrapped around the anastomotic suture line.

Table 4: Number and Percentage of Patients with Anastomotic Leak–Related Abdominal Events. A Retrospective Analysis of the Use of Seprafilm at the Site of Bowel Anastomosis 30 Postoperative Days

Serious Adverse Events	Seprafilm on Bowel Anastomotic Suture Line (n=289 patients)	Seprafilm not on Bowel Anastomotic Suture Line (n=593 patients)	Control (n=909 patients)
	n (%) Patients with Event	n (%) Patients with Event	n (%) Patients with Event
Fistula[1]	11 (3.8)*	5 (0.8)	2 (0.2)
Leak	20 (6.9)*	13 (2.2)	16 (1.8)
Abdominopelvic abscess[2]	16 (5.5)*	14 (2.4)	27 (3.0)
Peritonitis	14 (4.8)*	12 (2.0)	12 (1.3)
Sepsis	10 (3.5)*	7 (1.2)	9 (1.0)
Patients ≥1 event	37 (12.8)*	31 (5.2)	45 (5.0)

* Statistically significant difference from control group detected (p<0.05).
[1] Fistula includes fistula and intestinal fistula.
[2] Abdominopelvic abscess category includes abscesses in the abdominal and pelvic cavities.

In the retrospective analysis, the incidence of serious abdominal adverse events (fistula, leak, peritonitis, sepsis, and abdominopelvic abscess) when using Seprafilm wrapped directly around the anastomotic suture or staple line was statistically greater than in the control group. The total incidence of serious abdominal adverse events when using Seprafilm not wrapped at the anastomosis was not statistically different from the control group.

During postmarketing experience, the following adverse reactions have been reported in patients receiving Seprafilm Adhesion Barrier: abscess, anastomotic leak, fistula, foreign body (fibrotic) reaction, hypersensitivity, inflammation, intra-abdominal fluid collection, peritonitis, postprocedural wound infection/wound dehiscence, sepsis, bowel obstruction, and fever.

DIRECTIONS FOR GENERAL USE

The Seprafilm Adhesion Barrier should not be used in altered physical forms, other than cutting to conform to anatomical requirements.

1. Seprafilm Adhesion Barrier should be applied immediately prior to abdominopelvic cavity closure following laparotomy.
2. Seprafilm Adhesion Barrier must be kept dry prior to application.
3. The surgical field, especially desired site of application, should be as dry as possible. Thoroughly aspirate excess fluid.
4. Open the foil pouch immediately prior to application and drop the interior sterile polyolefin sleeve containing Seprafilm Adhesion Barrier on the dry sterile field.
5. Remove the holder containing Seprafilm Adhesion Barrier from the polyolefin sleeve.
6. Where applicable, cut membrane and holder with scissors to desired size and shape.
7. The membrane should be handled gently with dry instruments and/or gloves.
8. Expose 1-2 cm of the membrane through the open end of the holder.
9. When necessary, facilitate entry into the abdominopelvic cavity by slightly curving or arching the membrane/holder.
10. When applying, avoid contact with tissue surfaces until directly at site of application. If contact occurs, moderate application of standard irrigation solution may be used to gently dislodge membrane from unintended tissue surfaces.
11. Allow exposed Seprafilm Adhesion Barrier to first adhere to desired position on the tissue or organ by gently pressing the membrane down with a dry glove or instrument and then withdraw the holder.
12. Extend Seprafilm Adhesion Barrier sufficiently beyond the margins of incision and associated surgical trauma to achieve adequate coverage.
13. When necessary, lightly moisten membrane with standard irrigation solution to facilitate its coverage around the contours of tissues or organs.
14. The number of sheets used should be just adequate to cover the undersurface of the abdominal wall or uterine incision in a single layer.

AFTER PLACEMENT

1. Discard holder(s) following application.
2. Care should be taken not to disturb the Seprafilm Adhesion Barrier once it is placed on the tissue.
3. Do not suture the Seprafilm Adhesion Barrier in place.
4. Abdominopelvic cavity should be closed according to the standard technique of the surgeon.

HOW SUPPLIED

Seprafilm Adhesion Barrier is packed in a Tyvek® holder within a plastic sleeve and packed in an outer sealed foil pouch. The contents of the foil pouch are sterilized by gamma radiation.

Refer to package label for film size and quantity.

Seprafilm Adhesion Barrier should be stored between 36°F-86°F (2°C-30°C).

CAUTION

Federal law restricts this device to sale by or on the order of a physician.

CLINICAL STUDIES

The safety and effectiveness of Seprafilm Adhesion Barrier have been evaluated in several studies. Initial multicenter safety studies have been performed in abdominal and gynecologic surgical procedures enrolling a total of 32 treatment and control patients.

No serious adverse events were definitely attributed to the use of Seprafilm Adhesion Barrier in these studies. Vital signs and laboratory values showed no clinically relevant differences between treatment and control groups.

A randomized, masked, multicenter clinical study involving 183 patients was conducted to evaluate the safety and effectiveness of Seprafilm Adhesion Barrier in ulcerative colitis and familial polyposis patients undergoing abdominal surgery. Seprafilm Adhesion Barrier was applied directly on the omentum and bowel to separate tissues from the overlying abdominal wall and midline incision. Patients enrolled were undergoing major abdominal surgery involving colectomy followed by ileal pouch anal anastomosis and formation of a temporary loop ileostomy. During the ileostomy closure several weeks later, the incidence, extent, and severity of adhesions to the midline incision were evaluated.

In the abdominal study, the incidence of adhesions to the area of membrane use, the midline incision was 94% (n=85) in control patients and 49% (n=42) in patients treated with Seprafilm Adhesion Barrier (p<0.0001). An absence of adhesions was observed in 51% (n=43) of patients treated with Seprafilm Adhesion Barrier and 6% (n=5) of control patients. The mean extent of adhesions (percentage of the incision length involved) among Seprafilm Adhesion Barrier patients was 23% (n=85) compared to 63% (n=90) in the control group (p<0.0001). A comparative analysis of the severity* of adhesions demonstrated the presence of dense adhesions occurring in 58% (n=52) of the control group and in 15% (n=13) of the Seprafilm Adhesion Barrier group. Overall, the adhesions in the Seprafilm Adhesion Barrier group were significantly less severe than in the control group (p<0.0001).

A second randomized, masked, multicenter clinical study involving 127 women was conducted to evaluate the safety and effectiveness of Seprafilm Adhesion Barrier on serosal tissue and pelvic organ structures deep in the pelvis in patients undergoing gynecologic surgery. Seprafilm Adhesion Barrier was applied to the anterior and posterior surfaces of the uterus following a myomectomy via laparotomy. Postoperative adhesion formation was evaluated during a second-look laparoscopy performed an average of 23 days later. The incidence of adhesions to the uterus (number of abdominopelvic locations adherent to the uterus) in patients treated with Seprafilm Adhesion Barrier was 4.98 (n=49) compared to control values of 7.88 (n=48) (p<0.0001). The severity** of adhesions was reduced from 2.43 (n=65) in the control group to 1.94 (n=54) in the Seprafilm Adhesion Barrier group (p<0.01). Reduction in extent scores from 1.68 (n=65) to 1.23 (n=54) (p<0.01) were also demonstrated in the control and Seprafilm Adhesion Barrier groups, respectively. The area of the uterus associated with adhesions was reduced from 18.72 (n=54) to 13.23 (n=65) in the patients treated with Seprafilm Adhesion Barrier versus control patients (p<0.02). The portion of patients with adnexal adhesions to the posterior uterus was reduced from 69% (n=45) to 52% (n=28) in patients with Seprafilm Adhesion Barrier compared to control patients (p<0.01).

A controlled, randomized postmarket approval study involving 1791 patients (1701 undergoing intestinal resection and 90 patients undergoing adhesiolysis for existing SBO) was conducted to evaluate the safety and effectiveness of Seprafilm in reducing bowel obstructions. In this study, application of Seprafilm to a fresh anastomosis was optional. Up to 10 membranes (mean of 4.4, median of 4.0, and range of 0.5 to 10) were applied to the organs and tissues that sustained direct surgical trauma, or were potentially adhesiogenic. All patients were followed for incidence of bowel obstructions until study completion at 5 years for a mean of 3.4 year follow up (median of 3.4 years and a range of 3 days to 5.0 years).

Using protocol defined criteria, 15 of the 840 intestinal resection patients (1.8%) in the Seprafilm group experienced an adhesive SBO that required reoperation compared to 29 of 861 intestinal resection patients (3.4%) in the control group (p<0.05). When all cases of bowel obstruction were considered, including those in which bowel obstruction could not be ruled out, 109 of 888 patients (12%) in the Seprafilm group and 106 of 903 patients (12%) in the control group had bowel obstruction. Of the 90 patients with existing bowel obstructions, no significant difference in incidence of adhesive SBO requiring reoperation was found (3 of the 48 Seprafilm patients versus 1 of 42 control patients).

* Severity is defined as: (1) filmy thickness, avascular; (2) moderate thickness, limited vascularity; or (3) dense thickness, vascularized.
** Severity is defined as: (0) no adhesion present; (1) filmy avascular; (2) some vascularity; (3) cohesive

REFERENCES

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2. Becker JM, Dayton MT, Fazio VW, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. *J Am Coll Surg*. 1996;183(4):297-306.
3. Burns JW, Cox S, Walts AE. Water insoluble derivatives of hyaluronic acid. US patent 5 017 229. May 21, 1991.
4. Diamond MP, for the Seprafilm Adhesion Study Group. Reduction of adhesions after uterine myomectomy by Seprafilm® membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. *Fertil Steril*. 1996;66(6):904-910.
5. Fazio VW, Cohen Z, Fleshman JW, et al. Reduction in adhesive small-bowel obstruction by Seprafilm adhesion barrier after intestinal resection. *Dis Colon Rectum*. 2006;49(1):1-11.

SYMBOLS USED IN LABELING:

Symbol	Symbol Title and Description	Symbol Reference
REF	Catalogue number; Indicates the manufacturer's catalogue number so that the medical device can be identified.	ISO 15223-1:2016, 5.1.6
LOT	Batch code; Indicates the manufacturer's batch code so that the batch or lot can be identified.	ISO 15223-1:2016, 5.1.5
	Use-by date; Indicates the date after which the medical device is not to be used.	ISO 15223-1:2016, 5.1.4
http://edocs.baxter.com	Consult instructions for use; eIFU indicator; Indicates the need for the user to consult the instructions for use electronic location.	ISO 15223-1:2016, 5.4.3
Rx Only	Caution: Federal law restricts this device to sale by or on the order of a physician.	21 CFR 801

U.S. Only: These instructions are available electronically at http://edocs.baxter.com

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