ADHESION BARRIER

CHEMICALLY MODIFIED SODIUM HYALURONATE/ CARBOXYMETHYLCELLULOSE

ABSORBABLE ADHESION BARRIER

MANUFACTURED BY: Genzyme Biosurgery
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SEPRAFILM® ADHESION BARRIER

DESCRIPTION: Seprafilm® Adhesion Barrier (membrane) is a sterile, biodegradable, 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-ethylcarboxymethylidene chloride (EDC). Seprafilm should be stored between 36-86°F (2-30°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 under-lying 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.

CONTRAINDICATIONS: 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 post-approval study when Seprafilm Adhesion Barrier was wrapped directly around a fresh anastomotic suture or staple line.

A mean of two of the 5” x 6” Seprafilm membranes were applied to patients in the two pre-market studies. In the post-market 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 post-market 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 post-market 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 pre-market trials (Tables 1 and 2) and the post-market 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

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Seprafilm Membrane N=91</th>
<th>Control N=92</th>
<th>Seprafilm Membrane N=91</th>
<th>Control N=92</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileus and Fever</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Rectovaginal Fistula</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Pulmonary Embolus</td>
<td>4%</td>
<td>5%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea/Vomiting/Diarrhea</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Intra-abdominal Bleeding</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Myocardial Infarction/Death</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Mesenteric Thrombus</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Ventricular Arrhythmia</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Large Blood Clot/Rectum</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Pouchitis</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Rectovaginal Fistula</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Seprafilm Membrane N=59</th>
<th>Control N=68</th>
<th>Seprafilm Membrane N=59</th>
<th>Control N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Myomectomy Patients</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ileus and Fever</td>
<td>2%*</td>
<td>0%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Fever-Blood Typing Error</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Laparoscopy Converted to Laparotomy</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Intra-abdominal Bleeding</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Atelectasis and Ileus</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Postoperative Fever</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
</tbody>
</table>

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

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.
Intestinal Obstruction 1 38 (4) 33 (4) 65 (7) 68 (8)  
Intra-abdominal Fluid Collection 9 (1) 6 (1) 11 (1) 6 (1)  
Ileus 40 (5) 40 (4) 51 (6) 46 (5)  
GI Hemorrhage 9 (1) 3 (<1) 13 (2) 8 (1)  
Vomiting 13 (2) 13 (1) 22 (3) 20 (2)  
Fistula 4 16 (2*) 21 (6*) 7 (1)  
Vomiting 13 (2) 13 (1) 22 (3) 20 (2)  
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 Intestinal Obstructions were spontaneously reported obstructions of all causes during the post-operative 30 day period.  
2 Abdominopelvic Abscesses included abdominal abscesses and pelvic abscess.  
3 Postoperative Wound Infection included postoperative wound infection and wound abscess.  
4 Fistula includes fistula and intestinal fistula.  
5 Wound Dehiscence included fascial wound dehiscence, superficial wound dehiscences, and wound dehiscence.  

2. Seprafilm Adhesion Barrier must be kept dry prior to application.  
3. Remove the holder containing Seprafilm Adhesion Barrier.  
4. Extend Seprafilm Adhesion Barrier sufficiently beyond the margins of incision and orient the barrier as needed.  

DIRECTIONS FOR GENERAL USE:  
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 polyethylene sleeve containing Seprafilm Adhesion Barrier on the dry sterile field.

**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 36-68°F (2-23°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 the tissues from the underlying abdominal wall and midline incision. Patients enrolled were undergoing major abdominal surgery involving colorectal surgery followed by pouch 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<0.001).

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=53) in the control group to 1.23 (n=52) in patients treated with Seprafilm Adhesion Barrier (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 1.72 (n=65) to 1.32 (n=54) (p<0.05) and the area associated with adhesions in the control group was significantly less than in the control group (p<0.02).

A controlled, randomized post-market 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. Adhesions were followed for incidence of bowel obstruction 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 adverse 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 definitely attributed to SBO, 129 of 888 patients (14%) in the Seprafilm 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 adhesions SBO requiring reoperation was found.
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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