GYNECARE INTERGEL* Adhesion Prevention Solution
(0.5% Ferric Hyaluronate Gel)

Caution: Federal (U.S.) law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

1. DEVICE DESCRIPTION

GYNECARE INTERGEL Adhesion Prevention Solution (GYNECARE INTERGEL Solution) is a sterile, nonpyrogenic, amber colored, viscous solution of sodium hyaluronate, which has been ionically crosslinked with ferric ions and provides a transient viscous, lubricious coating on the peritoneal surfaces following surgical procedures.

GYNECARE INTERGEL Solution is packaged in a 300 mL low density polyethylene bellows-type bottle, which is provided sterile in a plastic tray using a Tyvek® lid. When stored at refrigerated (2-8 °C) or controlled room temperature (15 - 30°C), INTERGEL has a stable shelf life of 24 months.

2. INTENDED USE/INDICATIONS

GYNECARE INTERGEL Adhesion Prevention Solution is indicated for use in patients undergoing open, conservative gynecologic surgery as an adjunct to good surgical technique to reduce post-surgical adhesions. GYNECARE INTERGEL Adhesion Prevention Solution is also intended to reduce the likelihood of developing moderate or severe postoperative adnexal adhesions in these patients.

3. CONTRAINDICATIONS

- GYNECARE INTERGEL Solution is contraindicated in patients with pelvic or abdominal infection.

4. WARNINGS

- The safety and effectiveness of GYNECARE INTERGEL Solution has not been established in patients undergoing any procedures other than class I, non-oncologic, pelvic gynecologic laparotomy.

- The safety and effectiveness of GYNECARE INTERGEL Solution has not been established in patients undergoing laparoscopy procedures. Two randomized non-blinded clinical investigations of GYNECARE INTERGEL Solution in laparoscopy failed to

demonstrate effectiveness via this route of installation in gynecologic surgery.

- The safety and effectiveness of GYNECARE INTERGEL Solution has not been studied in cancer patients.
- The safety and effectiveness of GYNECARE INTERGEL Solution has not been studied in patients undergoing hysterectomy procedures or any procedure in which an organ is removed.
- In clinical studies of GYNECARE INTERGEL Solution, 300 mL of solution per patient were instilled into the peritoneal cavity, not adjusted for patient weight. The safety and effectiveness of larger or smaller volumes have not been established.
- Foreign body reactions may occur with GYNECARE INTERGEL Solution as with any implanted material.
- The safety and effectiveness of GYNECARE INTERGEL Solution has not been studied in patients with a history of hemochromatosis, or in patients who are unable to process large fluid loads, such as patients with congestive heart failure.

5. PRECAUTIONS

Caution: The safety and effectiveness of GYNECARE INTERGEL Solution in combination with other adhesion prevention products, peritoneal instillates, absorbable hemostats and/or medications administered within the abdominopelvic cavity have not been established in clinical studies.

Caution: The safety and effectiveness of GYNECARE INTERGEL Solution has not been evaluated in patients less than 18 years of age.

Caution: Clinical studies have not been conducted in pregnant women or women who have become pregnant within the first month after exposure to GYNECARE INTERGEL Solution. Therefore, this product is not recommended for use during pregnancy. Following the use of GYNECARE INTERGEL Solution, it is advised to avoid conception during the first complete menstrual cycle.

Caution: GYNECARE INTERGEL Solution has not been studied in patients with significant hepatic or renal disorders nor in patients having surgery which involves opening of the gastrointestinal or urinary tract.

Caution: GYNECARE INTERGEL Solution has not been studied in patients who have lymphatic, hemotologic or coagulation disorders, or patients taking coagulants.

Caution: GYNECARE INTERGEL Solution has not been studied in patients who are taking oral or parental hypoglycemic agents for diabetes.

Caution: GYNECARE INTERGEL Solution has not been studied in patients who are immunocompromised or have autoimmune disorders.

Caution: Long-term clinical outcomes such as chronic pain, infertility, and small bowel obstruction have not been determined in clinical studies.

6. ADVERSE REACTIONS

Table 1 reports the local (surgical site) adverse events observed in patients treated with GYNECARE INTERGEL Solution during an international, randomized, double-masked, multi-center study comparing the safety and effectiveness of GYNECARE INTERGEL Solution (300 mL) and lactated Ringer's solution (300 mL) in 281 patients (GYNECARE INTERGEL Solution: 143 patients; lactated Ringer's solution: 138 patients).

Table 1: Local (Surgical Site) Adverse Events

	Intergel	Control
# Patients Enrolled	143	138
Incision inflammation	8 (5.6%)	8 (5.8%)
Incision opening	7 (4.9%)	5 (3.6%)
Pain:		
Incisional	9 (6.3%)	13 (9.4%)
Abdominal	39 (27.3%)	42 (30.4%)
Pelvic	3 (2.1%)	3 (2.2%)
Back	13 (9.1%)	7 (5.1%)
Infection:	8[a] (5.6%)	4[b] (2.9%)
Possibly device related (Investigator assessment)	3[c] (2.1%)	1[d] (0.7%)

[a] bladder; wound(2); pelvic/wound; unspecified(2); chlamydia; vaginal
[b] wound(2); unspecified; vaginal
[c] bladder; pelvic/wound; unspecified
[d] wound

Table 2 reports systemic adverse events observed in 5% or more of the study patients.

Table 2: Systemic Adverse Events Reported Greater than 5%, Number (%) of Patients

Body System Preferred Term	INTERGEL (N=143)	lactated Ringer's Solution (N=138)
Body as a Whole	**143 (100)**	**137 (99.3)**
Pain	122 (85.3)	111 (80.4)
Headache	45 (31.5)	37 (26.8)
Fever	25 (17.5)	19 (13.8)
Allergic reaction	3 (2.1)*	10 (7.2)
Digestive	**106 (74.1)**	**100 (72.5)**
Nausea	66 (42.6)	65 (47.1)
Constipation	47 (32.9)	56 (40.6)
Flatulence	35 (24.5)	35 (25.4)
Vomiting	13 (9.1)	14 (10.1)
Dyspepsia	14 (9.8)	10 (7.2)
Urogenital	**44 (30.8)**	**40 (29.0)**
Dysmenorrhea	25 (17.5)	22 (15.9)
Nervous	**37 (25.9)**	**40 (29.0)**
Insomnia	20 (14.0)	22 (15.9)
Dizziness	15 (10.5)	13 (9.4)
Respiratory	**30 (21.0)**	**26 (18.8)**
Cough, increased	11 (7.7)	8 (5.8)
Rhinitis	8 (5.6)	7 (5.1)
Cardiovascular	**15 (10.5)**	**15 (10.9)**
Tachycardia	4 (2.8)	7 (5.1)
Hemic and Lymphatic	**19 (13.3)**	**16 (11.6)**
Anemia	12 (8.4)	13 (9.4)
Skin	**13 (9.1)**	**13 (9.4)**
Pruritus	8 (5.6)	10 (7.2)

*p = 0.048, Fisher's Exact test.

In one randomized non-blinded laparoscopy trial of patients in the United States (221 subjects), wound infections were reported for 5 GYNECARE INTERGEL Solution patients (4.4%) and no patients (0.0%) in the control group (lactated Ringer's solution). There was one report of a possible, post-operative pelvic infection in the control group (1.0%). In a similar randomized non-blinded laparoscopy trial in Europe (144 patients), there were 5 reports of possible, post-operative pelvic infection (6.8%) in the GYNECARE INTERGEL Solution patients, and one report (1.4%) in the control group.

7. CLINICAL STUDIES

GYNECARE INTERGEL Solution has been studied in a pilot study and pivotal study in female patients undergoing peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy. The purpose of these studies was to evaluate the safety and effectiveness of the device in reducing post-surgical adhesions. Patients were administered 300 mL of GYNECARE INTERGEL Solution or lactated Ringer's Solution as an intraperitoneal instillate at the completion of the laparotomy procedure. Adhesions were assessed at prospectively determined anatomic sites, using prospective scales for extent and severity, before and after adhesiolysis at baseline laparotomy, and at second look laparoscopy. Safety was assessed based on adverse events recorded throughout the study, on clinical laboratory tests performed at baseline and post-therapy, and on gross evaluation at second-look.

The pilot study was a randomized, unmasked, single investigator / single center trial of 23 patients to evaluate the preliminary safety and use of 300cc GYNECARE INTERGEL Solution compared to 300cc lactated Ringers control in female patients undergoing laparotomy for infertility. The pilot study enrolled 23 women, aged eighteen to forty-five year, undergoing limited, class 1 (clean), open peritoneal cavity surgery. The most common procedures were adhesiolysis and myomectomy performed for infertility. A total of 21 patients, 11 treatment and 10 control, completed the second look laparoscopy at 4 to 12 weeks after the initial surgery as part of the treatment plan. Eighteen pre-specified anatomic sites for adhesion incidence, extent and severity, as well as any other co-incident effects were evaluated during the second look laparoscopy. The mean incidence of baseline adhesions was 3.55 $\pm$ 4.52 for the 11 GYNECARE INTERGEL Solution patients and 4.33 $\pm$ 3.93 for the 9 control patients. (One control patient who had 17 adhesions at baseline, all of which reformed, was excluded from the analysis). At second look laparoscopy, the mean incidence of sites with adhesions was 6.09 $\pm$ 4.59 for the INTERGEL Solution patients and 11.00 $\pm$ 3.24 for the control patients (p=0.015). The safety profile was comparable for the 2 groups.

The pivotal study was a randomized, multi-center, masked clinical study conducted at 11 US Centers and 5 European Centers in order to evaluate the safety and effectiveness of applying 300cc of GYNECARE INTERGEL Solution compared to 300cc of Lactated Ringers at the end of clean (no gastro-intestinal or genito-urinary tract breach; no infectious process), peritoneal cavity laparotomy procedures.

The study enrolled 281 patients who were otherwise healthy eighteen to forty-five year old women with limited adhesions (at less than twelve of twenty four sites), desiring to retain fertility, and expecting to undergo second look laparoscopy as part of their treatment plan at 6 to 12 weeks. During second look laparoscopy, 265 patients were evaluated at twenty-four pre-specified anatomic sites for adhesion incidence, severity and extent, as well as any other co-incident effects. Results are reported for adhesions present at second-look, including those that were not excised at surgery.

The primary endpoint for effectiveness was a Modified American Fertility Society (mAFS) score and the secondary effectiveness endpoints were proportion of sites with adhesions, adhesion extent and adhesion severity. A composite score of 0 to 16 was determined per anatomic site based on adhesion incidence, severity and extent at each site. Scores per anatomic site (23 sites at first look; 24 sites at second look) were combined to determine an adhesion final score per patient; the possible mAFS score range per patient was 0–16.

Table 3 provides the accounting and demographics for the pivotal study.

Table 3: Pivotal Study Patient Accounting and Demographics

	Intergel	Control
# treated	**143**	**138**
# with no second-look	**12***	**4**
# completed study	**131**	**134**
Demographics:		
Race, n (%)		
Caucasian	74 (56.5)	82 (61.2)
Black	28 (21.4)	23 (17.2)
Oriental	4 (3.1)	4 (3.0)
Hispanic	20 (15.3)	22 (16.4)
Other	5 (3.8)	3 (2.2)
Age, mean, sd	33.8 (5.8)	34.2 (5.4)
Weight, mean, sd	150.1 (30.9)	150.2 (31.8)
Baseline Adhesion #, mean (0-24)	**3.65**	**3.46**
Baseline mAFS, mean (0-16)	**1.07**	**1.07**
Blood loss (cc), mean (sd)	**214 (214)**	**224 (284)**
Operative Time (hrs), mean (sd)	**1.86 (0.82)**	**1.80 (0.85)**
Days to Discharge, mean (sd)	**3.0 (1.6)**	**3.0 (1.7)**
Days to second look, mean (sd)	**60.4 (26.2)**	**58.7 (21.4)**

*1 patient was lost to follow-up

The results for the primary effectiveness endpoint, mean mAFS, are presented below in Table 4.

Table 4: Primary Effectiveness Results, Mean mAFS (Range 0-16)

	Intergel	Control	p-value
N	131	134	
Baseline Score (Range 0-16)	1.07	1.07	0.870
2nd Look Score (Range 0-16)	1.36	2.32	0.002

An AFS score was calculated from mAFS score data using three sites for each ovary and two sites for each tube; the higher score of the right and left side was dropped; the lower score of the right and left side per patient became the AFS score per patient. Further analyses included shift tables in which the calculated AFS were stratified into segments and the shift from baseline to second look was tabulated. The effect that treatment had on the stratified AFS score is analyzed in Table 5 below.

Table 5.
Shift Table of Baseline and 2nd Look Stratified AFS Score

AFS Category Analysis		INTERGEL® Solution					Lactated Ringer's Solution					
			Second Look					Second Look				
		Baseline Total	Min. 0-5	Mild 6-10	Mod. 11-20	Sev. 21-32	Baseline Total	Min. 0-5	Mild 6-10	Mod. 11-20	Sev. 21-32	p
Minimal	0-5	109	103	4	1	1	109	96	6	3	4	
Mild	6-10	13	10	2	1	0	8	4	1	2	1	
Moderate	11-20	7	6	1	0	0	13	3	4	5	1	
Severe	21-32	2	2	0	0	0	4	2	1	0	1	
Total Second-look		131	121	7	2	1	134	105	12	10	7	0.001* 0.001**

Binary Analysis			Second Look			Second Look		p
		Baseline Total	Min./Mild 0-10	Mod./Sev. 11-32	Baseline Total	Min./Mild 0-10	Mod./Sev. 11-32	
Min./Mild	0-10	122	119	3	117	107	10	
Mod./Sev.	11-32	9	9	0	17	10	7	
Total Second Look		131	128	3	134	117	17	0.003
Relative Risk		(INTERGEL® Solution/Control): 0.195 95% CI: 0.065 to 0.583						

* p value determined using CMH test controlling for Baseline level (ridit scores)
**p value determined using CMH test controlling for Baseline level (median scores)

Analysis using the Cochran-Mantel-Haenszel test controlling for baseline level indicates a statistically significant p value (p=0.001) between treatment groups in the shift from one AFS adhesion category to another. Combining the minimal and mild categories, and the moderate and severe categories (binary analysis), at second-look there were 3 of 131 patients (2.3%) in the moderate/severe category compared to 17 of 134 control patients (12.7%; RR=0.195).

The secondary effectiveness outcomes are the mean incidence of adhesions (range of 0-24), extent of adhesions (range of 0-3), and severity of adhesions (range of 0-3)These baseline and second look laparoscopy results are provided in Table 6 below.

Table 6: Secondary Effectiveness Results

	Intergel	Control	p-value
N	131	134	
Baseline Incidence (Range 0-24)	3.65	3.46	0.744
2nd Look Incidence (Range 0-24)	6.56	7.63	0.096
Baseline Extent (Range 0-3)	0.29	0.30	0.964
2nd Look Extent (Range 0-3)	0.47	0.63	0.019
Baseline Severity (Range 0-3)	0.38	0.35	0.670
2nd Look Severity (Range 0-3)	0.52	0.73	0.007

8. HOW SUPPLIED

GYNECARE INTERGEL Solution is supplied in a sterile, single use, 320 mL bottle with an extension tube.

9. DIRECTIONS FOR USE

GYNECARE INTERGEL Solution, 300 mL, is administered into the peritoneal cavity following peritoneal cavity surgery, after the surgeon has aspirated all irrigants, and removed all packs and sponges.

GYNECARE INTERGEL Solution should be used at room temperature or warmed to body temperature prior to use. If GYNECARE INTERGEL Solution is warmed to body temperature, do not allow the product to remain at this temperature in excess of 24 hours as stability of the product cannot be assured.

1. Transfer the GYNECARE INTERGEL Solution to the sterile field using standard aseptic operating room technique and twist the tab to remove it from the bottle.

2. To facilitate surgical site-specific coverage, an extension tube is provided. Firmly attached the extension tube to the bellows container while supporting the nozzle at its base.

   - Grip the bellows container with the heel and/or thumb of each hand at the base and fingers at the top of the container. Dispense the GYNECARE INTERGEL Solution directly into the peritoneal cavity by collapsing the bellows container. Dispense in a manner that the GYNECARE INTERGEL Solution covers all operative sites.

   - After dispensing approximately one-third (1/3) of the contents of the bellows container, allow the bellows container to equilibrate with air and re-acquire its initial shape.

   - Roll the bellows container in a circular motion to collect droplets of product clinging to the sides of the container. Continue to alternate between dispensing product, and allowing the bellows container to equilibrate with air.

   - Dispense the remainder of the 300 mL of GYNECARE INTERGEL Solution. It will be noted that some excess will remain in the bottle.

3. Alternatively, the GYNECARE INTERGEL Solution can be dispensed into a sterile basin and applied using a cannula syringe and cannula of at least 5 mm diameter.

Note: *Special attention should be given to ensure the gel has covered sites such as the ovarian fossa and rectosigmoid where peritoneal circulation may be limited. Distribution can be facilitated by the surgeon's hand, probe or extension tube.*

10. STORAGE

GYNECARE INTERGEL Solution should be stored at refrigerated or controlled room temperature (2-30°C which is 36-86°F). DO NOT FREEZE.

11. STERILITY

GYNECARE INTERGEL Solution is sterilized by filtration and aseptically processed. The primary container (bellows bottle) is sterilized by hydrogen peroxide gas plasma. Do not resterilize. Do not use if package is opened or damaged. Discard open, unused product.

STERILE SINGLE USE ONLY

CAUTION: Federal Law restricts this device to sale by or on the order of a physician.

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