Baxter

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adept®

Adhesion Reduction Solution (4% Icodextrin)

INFORMATION FOR PRESCRIBERS

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN.

CAUTION: DO NOT USE UNLESS SOLUTION IS CLEAR AND CONTAINER IS UNDAMAGED.

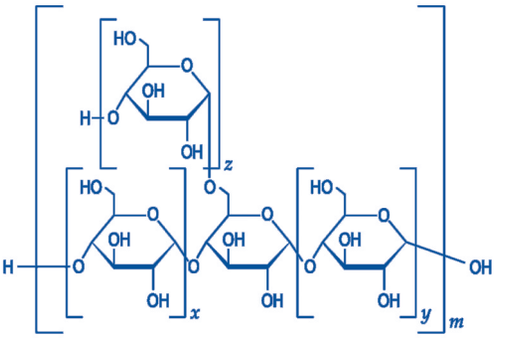
CAUTION: ADEPT® is for direct intraperitoneal administration only. **NOT** FOR INTRAVENOUS (IV) ADMINISTRATION.

I. DEVICE DESCRIPTION AND MECHANISM OF ACTION

ADEPT® (4% Icodextrin) Adhesion Reduction Solution is a single use, sterile, clear, colorless-to-pale yellow fluid for intraperitoneal administration containing icodextrin at a concentration of 4% w/v in an electrolyte solution. Icodextrin is a cornstarch-derived, water-soluble branched glucose polymer linked by alpha (1 – 4) and less than 10% alpha (1 – 6) glucosidic bonds with a weight-average molecular weight between 13,000 and 19,000 Daltons and a number-average molecular weight between 5,000 and 6,500 Daltons.

The representative structural formula of icodextrin is:

Figure 1: Structural Formula of Icodextrin



Each 1 liter of ADEPT® contains:

Icodextrin	40 g
Sodium Chloride	5.4 g
Sodium Lactate	4.5 g
Calcium Chloride	257 mg
Magnesium Chloride	51 mg

Theoretical osmolarity 278 milliosmoles per liter

Ionic composition (approximately) per liter:

Sodium	133 mmol
Calcium	1.75 mmol
Magnesium	0.25 mmol
Chloride	96 mmol
Lactate	40 mmol

ADEPT® is packaged in flexible polyvinylchloride bags containing 1.5 L of solution. When stored at temperatures below 30°C ADEPT® has a shelf life of 24 months. ADEPT® should not be refrigerated or frozen.

MECHANISM OF ACTION AND CLEARANCE

Icodextrin, as an alpha (1 – 4)-linked glucose polymer, is similar in structure to carbohydrates which occur physiologically, e.g. glycogen. When administered intraperitoneally as a 4% solution, icodextrin functions as a colloid osmotic agent. This colloidal osmotic action of icodextrin allows the retention of a reservoir of fluid within the peritoneal cavity for 3 – 4 days.[1]

ADEPT® is believed to perform its function through a physical effect by providing a temporary separation of peritoneal surfaces by hydroflotation as a result of maintaining a fluid reservoir. This minimizes tissue apposition during the critical period of fibrin formation and mesothelial regeneration following surgery, thereby providing a barrier to adhesion formation.

Pharmacokinetics of Icodextrin

Absorption

Absorption of icodextrin from the peritoneal cavity follows zero-order kinetics, consistent with convective transport via the lymphatic pathways. Studies in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) indicate that a median of 40% of the instilled icodextrin was absorbed from the peritoneal solution during a 12 hour dwell.[2]

Metabolism and Elimination

When given intraperitoneally, the icodextrin polymer is not metabolized significantly in the peritoneal cavity but is slowly transferred into the systemic circulation by peritoneal lymphatic drainage. In the systemic circulation icodextrin is rapidly metabolized by alpha-amylase to lower molecular weight oligosaccharides, which along with icodextrin, are eliminated by renal excretion. The rate of clearance of icodextrin from the systemic circulation has been estimated to be equal to glomerular filtration rate.

II. INDICATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

INDICATION FOR USE

ADEPT® Adhesion Reduction Solution is indicated for use intraperitoneally as an adjunct to good surgical technique for the reduction of post-surgical adhesions in patients undergoing gynecological laparoscopic adhesiolysis.

CONTRAINDICATIONS

ADEPT® is contraindicated:

- In patients with known or suspected allergy to cornstarch based polymers e.g. icodextrin, or with maltose or isomaltose intolerance, or with glycogen storage disease.
- In the presence of frank infection (e.g. peritonitis) in the abdominopelvic cavity.
- In procedures with laparotomy incision. Serious post-operative wound complications including dehiscence and cutaneous fistula formation have been reported from clinical experience outside the US when ADEPT® was used in surgical cases with laparotomy incision.
- In procedures involving bowel resection or repair, or appendectomy. Anastomotic failure, ileus and peritonitis following procedures involving bowel resection and instillation of ADEPT® have been reported from clinical experience outside of the US.

WARNINGS

- There have been rare reports of sterile peritonitis following the use of icodextrin. The differential diagnosis of abdomino-pelvic pain following instillation of ADEPT® should include peritoneal cavity infection, perforated bowel or other viscous, intraperitoneal bleeding, and other life threatening post-operative complications in addition to sterile peritonitis.
- Leaking ADEPT® fluid through laparoscopic port sites post-operatively is associated with wound complications such as subcutaneous fluid collection, skin separation and infection. Meticulous closure of fascia may help reduce wound complications related to fluid extravasation following gynecologic laparoscopy surgery.
- There have been rare reports of hypersensitivity reactions in patients treated with ADEPT®. Anaphylaxis has been reported in a few patients.
- There are rare reports of pulmonary edema, pulmonary effusion and arrhythmia from clinical experience with ADEPT® outside of the US. These cases tended to occur in elderly or otherwise debilitated patients (e.g. cancer patients). The potential benefit of ADEPT® for adhesion prevention should be carefully weighed against the risk of serious complications in patients with serious co-morbidities.
- Foreign body reactions may occur with ADEPT®, as with any implanted material.

PRECAUTIONS

- ADEPT® is for direct intraperitoneal administration only. **NOT** for intravenous (IV) administration.
- ADEPT® is not indicated as a delivery system for intraperitoneal drugs such as antibiotics and chemotherapeutic agents.
- The effectiveness of ADEPT® has not been established for longer term clinical outcomes following gynecological surgery, e.g. pregnancy and pain.
- Self-limited vulvar swelling is a known side-effect of instilling large volumes of fluid into the abdomino-pelvic cavity. Most cases resolve within one week of surgery. When swelling is associated with urinary retention, catheterization may be necessary.
- Maltose metabolites of icodextrin may interfere with blood glucose measurement in diabetic patients who use rapid blood glucose systems that are not glucose specific.

- The safety and effectiveness of ADEPT® have not been evaluated:
- in patients less than 18 years of age;
- in pregnancy;
- when volume left in peritoneal cavity exceeds 1 L;
- in patients with abnormal liver and/or renal function; or
- in cases where there is a breach in the vaginal epithelium;

III. ADVERSE EVENTS

Postmarketing Passive Surveillance Outside of US

ADEPT® Adhesion Reduction Solution was approved for use in Europe in October 1999. A Europe-wide multicenter registry for evaluating clinical experience using ADEPT® was launched in 2000. The ARIEL registry was intended to capture the experience of surgeons using ADEPT® in both general and gynecological surgery. Data were collected between September 2000 and December 2003.

A total of 4620 patients were enrolled in the ARIEL registry. Of these, 2882 were gynecology patients (72% laparoscopy) and 1738 were general surgery patients (85% laparotomy). Adverse events were reported in 7.5% gynecological laparoscopy and 13.9% gynecological laparotomy patients compared with 16.7% general surgery laparoscopy and 30.6% general surgery laparotomy patients.[3, 4] Table 1 summarizes key events. These events are presented regardless of the reporting surgeon's causality assessment.

Table 1. Selected Key Adverse Events from ARIEL Registry[a]

	Gynecology N=2882			General Surgery N=1738		
Adverse Event	**Laparo-scopy**	**Laparo-tomy**	**Not known**	**Laparo-scopy**	**Laparo-tomy**	**Not known**
Wound Complica-tion[b]	13	15	1	2	68	4
Vulvar Swelling	7	1	3	0	1	0
Failed anasta-mosis	0	0	0	4	33	0
Ileus	3	2	1	4	46	1
Pain	15	10	2	4	9	0
Pulmonary Complica-tion	0	3	0	1	7	0
Allergic Reaction[c]	0	2	0	0	2	0

[a] Adverse events in this table were tabulated using a different methodology from that of Sutton[3] et al., and Menzies[4] et al. Therefore, numbers of events in different categories may not correspond exactly with the numbers in the published literature.

[b] "Wound complication" includes subcutaneous fluid collection near the incision/port site.

[c] Icodextrin has been associated with skin reactions such as rash. Three of the cases in the above table were more serious events and had systemic involvement.

US Clinical Trial Experience

ADEPT® has been studied in three randomized, controlled US clinical trials involving a total of 548 patients undergoing gynecological laparoscopic surgery with second look laparoscopy 4 – 12 weeks after the initial procedure. In all three studies, the control device was Lactated Ringer's Solution (LRS). Two pilot studies to obtain preliminary safety data enrolled a total of 99 (59 ADEPT® treated, 40 LRS) patients. The third US clinical trial of ADEPT® was a double-blind pivotal study in which 449 subjects (227 ADEPT® treated, 222 LRS) were treated.

Pilot Studies:

In the first pilot study (CLASSIC), 62 subjects (34 ADEPT® and 28 LRS) were evaluated. Approximately two liters of solution were used for irrigation intraoperatively, and one liter was instilled at the end of the procedure. Two cases of moderate labial or vulvar swelling were reported in the ADEPT® subjects. There were no LRS-related adverse events.

In the second pilot study (RAPIDS), 37 subjects (25 ADEPT® and 12 LRS) were evaluated. Approximately 1500 – 1900 mL of solution were used for irrigation intraoperatively. An average 2 L of ADEPT® vs. 1300 mL LRS was instilled at the end of the procedure. The objective of this study was to evaluate the safety of larger volumes of ADEPT® as a post-operative instillate. One case of labial swelling was reported in an ADEPT® subject.

Pivotal Clinical Trial:

In the double-blind, pivotal study, ADEPT® or LRS was used as an intraoperative irrigant (100 mL every 30 minutes) and 1 L was instilled into the peritoneal cavity at the end of the procedure. 221 (97.4%) ADEPT® patients reported a total of 1065 events compared to 218 (98.2%) LRS patients who reported 1047 events.

Table 2 presents adverse events reported in ≥5% of patients (regardless of causality) in the pivotal trial.

Table 2: Pivotal Study Most Frequent Adverse Events (i.e. those reported by at least 5% of patients in either group, regardless of causality) – Intention-to-Treat (ITT) Population

	ADEPT®		LRS	
	Number of patients reporting	Number of reports	Number of patients reporting	Number of reports
Total number of patients at risk	227		222	
Post procedural pain	192 (84.6%)	223	194 (87.4%)	233
Headache	81 (35.7%)	131	72 (32.4%)	127
Nausea	39 (17.2%)	41	37 (16.7%)	41
Leaking from Port Sites Post-procedure	31 (13.7%)	31	30 (13.5%)	30
Dysmenorrhea	30 (13.2%)	32	26 (11.7%)	34
Constipation	24 (10.6%)	26	23 (10.4%)	24
Pelvic pain	23 (10.1%)	32	21 (9.5%)	21
Arthralgia	20 (8.8%)	22	19 (8.6%)	19
Flatulence	19 (8.4%)	19	17 (7.7%)	19
Urinary tract infection	16 (7.0%)	17	12 (5.4%)	13
Abdominal pain	15 (6.6%)	26	19 (8.6%)	23
Dysuria	15 (6.6%)	16	8 (3.6%)	9
Nasopharyngitis	15 (6.6%)	15	18 (8.1%)	18
Vaginal bleeding	14 (6.2%)	15	5 (2.3%)	5
Abdominal distension	13 (5.7%)	13	10 (4.5%)	10
Post procedural nausea	13 (5.7%)	13	20 (9.0%)	20
Pyrexia	13 (5.7%)	13	7 (3.2%)	7
Vomiting	13 (5.7%)	13	22 (9.9%)	22
Labial, Vulvar or Vaginal swelling	13 (5.7%)	13	1 (0.45%)	1
Back pain	12 (5.3%)	15	12 (5.4%)	13
Insomnia	12 (5.3%)	14	8 (3.6%)	8
Cough	10 (4.4%)	10	12 (5.4%)	13
Diarrhea	3 (1.3%)	3	13 (5.9%)	15

In the pivotal study, the most frequently occurring (report incidence as % of number of patients) treatment-related adverse events between surgeries were post procedural leaking from port sites, labial, vulvar or vaginal swelling and abdominal distension.

IV. CLINICAL STUDIES

ADEPT® has been studied in the USA in two pilot studies and one doubleblind, pivotal study in female patients undergoing gynecological laparoscopic surgery with a planned second look laparoscopy. The studies were conducted to evaluate the safety and effectiveness of the device as an adjunct to good surgical technique in the reduction of post-surgical adhesions in comparison to (LRS). ADEPT® or LRS was used as an intra-operative irrigant (100 mL every 30 minutes) in all studies; in the pivotal study, 1 L of ADEPT® or LRS was instilled into the peritoneal cavity at the end of the surgical procedure. In the pilot studies, 1 L in the first study and up to 2 L in the second study were instilled at the end of surgery. In all three studies, the incidence, extent and severity of adhesions were assessed at 23 prospectively determined anatomical sites, using established adhesion scoring methods at baseline surgery (prior to adhesiolysis) and at second look laparoscopy. Safety was evaluated based on adverse events and clinical laboratory tests.

For both pilot studies, second look laparoscopy took place 6 – 12 weeks after the initial surgery. In both of these studies, there was a greater reduction in the number of sites with adhesions, and the extent and severity of adhesions in the ADEPT® subjects compared to the LRS subjects. However, these differences were not statistically significant, which may be due in part to the relatively small numbers of subjects in these studies.

PIVOTAL STUDY

The pivotal study was a comparative, double-blind, randomized, multicenter study in the USA. A total of 449 female patients aged eighteen or over were enrolled for whom laparoscopic peritoneal cavity surgery was planned for a gynecological procedure which included adhesiolysis and who agreed to undergo second look laparoscopy as part of their treatment plan at 4 – 8 weeks after the initial surgery. The patients had to have adhesions at three or more of the 23 pre-specified anatomical sites and adhesions at three or more of the anatomical sites had to be lysed during the surgery.

Objectives

The study objectives were to determine the effectiveness and safety of ADEPT® when used as an intraoperative washing solution with a postoperative instillate in the reduction of post-surgical adhesions after laparoscopic surgery for adhesiolysis, compared with LRS.

Inclusion Criteria:

- willing, able to and having freely given written consent to participate in the study and abide by its requirements;
- female patients aged eighteen and over, in good general health including ASA (American Society of Anesthesiologists) score of 2 or less;

- laparoscopic peritoneal cavity surgery is planned for a gynecologic procedure which includes adhesiolysis; and
- patient agrees to planned second look laparoscopy for this study 4 – 8 weeks after the initial surgical procedure.

Exclusion Criteria (pre-operative):

- current pregnancy including ectopic pregnancy;
- SGOT, SGPT and/or bilirubin >20% above the upper range of normal and considered clinically significant;
- BUN and creatinine >30% above the upper range of normal and considered clinically significant;
- concurrent use of systemic corticosteroids, antineoplastic agents and/or radiation;
- active pelvic or abdominal infection;
- known allergy to starch-based polymers; and
- additional surgical procedure (non-OB/GYN) planned to be performed during the laparoscopic procedure.

Exclusion Criteria (intra-operative):

- clinical evidence of cancer;
- clinical evidence of pregnancy including ectopic pregnancy;
- use during this procedure of any approved or unapproved product for the purpose of preventing adhesion formation;
- fewer than 3 of the available anatomical study sites contain adhesions;
- less than three of the anatomical sites are lysed;
- if the procedure needs to be performed by a laparotomy (decision made after laparoscopy has commenced);
- if any of the anatomical sites being scored for the purposes of this study are being removed during surgery;
- if all of the available anatomical sites cannot be visualized and recorded on the video tape during the surgery; and
- any unplanned surgery which involves opening of the bowel (excluding appendectomy).

Study Hypotheses

There were three co-primary outcome measures, each with a respective hypothesis:

(1) The first co-primary endpoint for the pivotal study was the difference (for an individual study subject) in the number of adhesion sites between baseline and second look laparoscopy. For subjects with ten or fewer adhesions lysed at surgery, an individual patient success was defined as a decrease of at least 3 sites with adhesions between baseline and second look laparoscopy. For subjects with more than ten adhesions lysed at baseline, individual patient success was defined as a decrease in adhesion sites of at least 30% between baseline and second look laparoscopy. The study hypothesis for the first co-primary endpoint was that the lower bound of the 95.2% CI around the difference in success rates will be above 5%.

(2) The second co-primary endpoint was the difference (for an individual study subject) in the number of adhesion sites between baseline and second look laparoscopy. In the hypothesis for this endpoint, patients served as their own control. The study hypothesis for the 2nd co-primary endpoint was that ADEPT® treated subjects would have fewer sites with adhesions at second look laparoscopy than they had at baseline.

(3) The third co-primary endpoint was the difference (for an individual subject) in the number of dense adhesion sites between baseline and second look laparoscopy. For the 3rd co-primary endpoint, success for a subject was defined as any reduction in dense adhesion sites between baseline and second look laparoscopy. The study hypothesis for the 3rd co-primary endpoint was that the success rate for ADEPT®-treated subjects would be greater than that for LRS treated subjects.

Secondary Endpoints

The study had the following pre-specified secondary endpoints.

No hypothesis tests were specified for these endpoints.

Incidence of sites with adhesions

Severity of sites with adhesions

Extent of sites with adhesions

American Fertility Society (AFS) score

Modified AFS score

Reformed adhesions

De novo adhesions

Abdominal wall adhesions

Visceral adhesions

Visual Analog Scale (VAS) score for pelvic pain

Figure 2 is a patient accounting of all subjects in the pivotal study, including the initial screen.

Figure 2: Patient Accounting

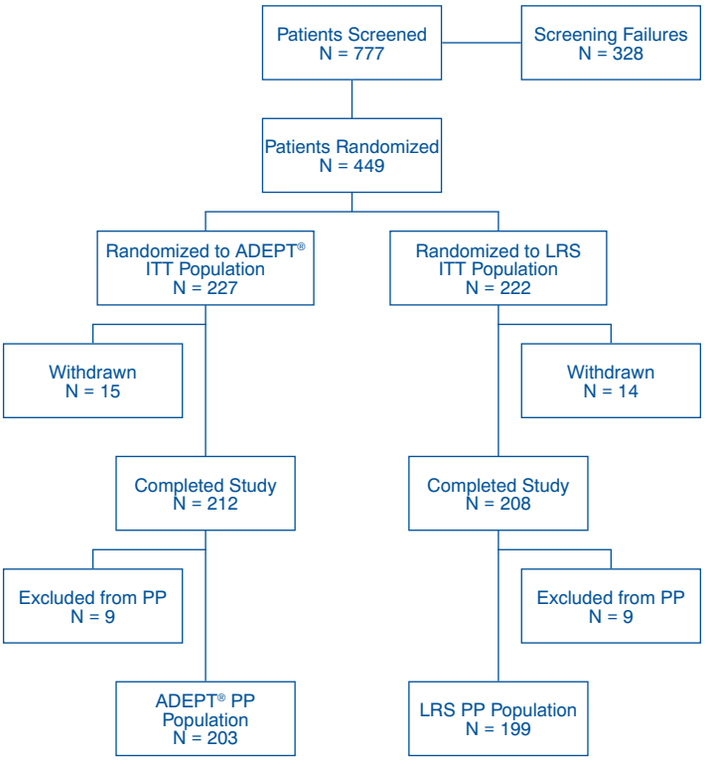


Table 3: Pivotal Study Demographics and Baseline Data, ITT

	ADEPT®	LRS
No. of patients randomized (ITT)	227	222
Demographics ± s.d.		
Age, yr	32.6 ± 5.9	32.3 ± 5.7
Height, in (n)	64.7 ± 2.7 (225)	64.2 ± 2.8 (221)
Weight, lb (n)	153.2 ± 36.9 (225)	152.0 ± 35.0 (220)
Race Caucasian	160 (70.5%)	144 (64.9%)
n (%): East Asian	3 (1.3%)	7 (3.2%)
African American	32 (14.1%)	32 (14.4%)
Hispanic	24 (10.6%)	35 (15.8%)
Oriental	3 (1.3%)	1 (0.5%)
Other	5 (2.2%)	3 (1.4%)
Base vital signs		
Systolic blood pressure, mmHg (n)	114.9 ± 12.1 (224)	114.5 ± 11.8 (221)
Diastolic blood pressure, mmHg (n)	71.5 ± 8.8 (224)	71.4 ± 8.8 (221)
Heart rate, bpm (n)	73.1 ± 8.8 (224)	73.2 ± 8.3 (218)
Primary diagnosis n (%)		
Pelvic pain	152 (67.0%)	134 (60.4%)
Endometriosis	94 (41.4%)	93 (41.9%)
Infertility	115 (50.7%)	127 (57.2%)
Adhesions	126 (55.5%)	127 (57.2%)
Others	36 (15.9%)	43 (19.4%)
Medical history n (%)		
No. of patients with resolved medical conditions	192 (84.6%)	191 (86.0%)
No. of patients with ongoing medical conditions	224 (98.7%)	219 (98.6%)
No. of patients with surgical history	205 (90.3%)	196 (88.3%)
Baseline assessment of adhesions		
Number of Sites with Adhesions	10.27 ± 4.26	10.34 ± 4.39
Number of Sites with lysed Adhesions	8.69 ± 4.15	8.46 ± 4.02
Number of Sites with dense Adhesions	6.17 ± 4.74	6.23 ± 5.26
Number of Sites with lysed dense Adhesions	5.35 ± 4.56	5.15 ± 4.46
Baseline AFS score for infertility subgroup (PP)	9.52 ± 10.39	8.60 ± 9.99
Baseline mAFS score (PP)	2.71 ± 2.47	2.81 ± 2.93
Endometriosis n (%)		
Present at baseline	140 (61.7%)	135 (60.8%)
Treated	138 (60.8%)	135 (60.8%)
Others		
Operative Time (mins) (median) (ITT)	85.0	88.0
Days between first and second look surgery (ITT)	39.9 ± 10.3	39.9 ± 10.7
Average volume of solution lavaged and instilled, ml (min-max)	3,502 (1,300-12,000)	3,570 (1,300-12,000)

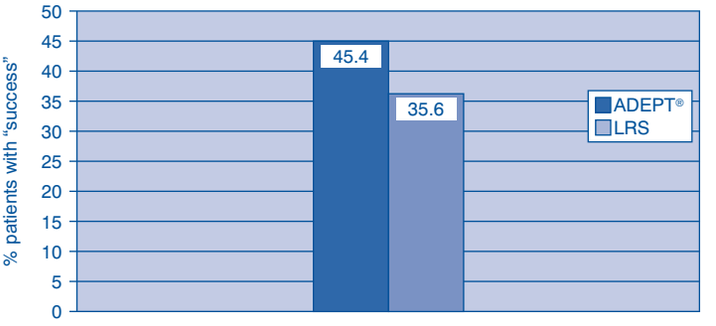
Table 3 shows that the study arms were well balanced. Almost all sites with adhesions were lysed (on average 10 at baseline with 9 lysed for both groups). Similarly, almost all sites with dense adhesions were lysed (on average 6 at baseline and 5 lysed). The study population had a fairly substantial adhesion burden with an average of 10 sites per subject and 6 sites with dense adhesions per subject.

Pivotal Study Results

Primary Effectiveness Endpoints

First Co-Primary Endpoint: 45.4% of the patients in the ADEPT® group were defined as a "clinical success" compared to 35.6% in the LRS group (p = 0.016, two-tailed test) (Table 4). However, the lower bound of the 95.2% CI around the difference in success rates (0.7%) is below the pre-specified 5% target. Data is presented as intent-to-treat (ITT). (see Figure 3.)

Figure 3: Pivotal Study First primary effectiveness endpoint (percentage of patients achieving "success") – Intention to Treat population



Second Co-Primary Endpoint: Patients in the ADEPT® group had significantly fewer sites with adhesions at second look compared to first look laparoscopy (p<0.001). The 95.2% confidence intervals were less than zero for both the ADEPT® treated patients (–2.83 to –1.62) and the LRS-treated patients (–2.24 to –0.96). There was a significantly greater reduction in the number of sites with adhesions in the ADEPT® treated patients compared with the LRS group (p = 0.047, two-tailed test).

Third Co-Primary Endpoint: In the ADEPT® group, 50% of patients had fewer sites with dense adhesions at second look (mean reduction 1.19 ± 3.43, p<0.001); in the LRS group, the figure was similar (49%) (see Table 4). There was no statistically significant difference between treatments (p = 0.73).

Table 4: Pivotal Study Primary Effectiveness Endpoints – Intention-to-Treat population

First primary effectiveness endpoint

	ADEPT®	LRS
Total number of patients	227	222
Success[a]		
Number reporting	103 (45.4%)	79 (35.6%)
Difference in % of patients with success	9.8	
Se	4.6	
95.2 CI for % of patients with success	**(0.7, 18.9)**	
Odds ratio[b]	1.64	
95.2% CI for odds ratio	(1.09, 2.46)	
p-value for treatment	0.016*	

a Success was achieved if the number of sites with adhesions decreased by at least the larger of three sites or 30% of the number of sites lysed

b Estimated from a logistic regression model with factors for treatment group and center. A value >1 favors ADEPT®. The odds ratio (95.2% CI) using exact methods was 1.61 (1.06, 2.46).

* Statistically significant at the 4.8% level, two-tailed

Second primary effectiveness endpoint

	ADEPT®	LRS
Total number of patients	227	222
Number of sites with adhesions		
First look (mean±sd)	10.27 ± 4.26	10.34 ± 4.39
Second look (mean ± sd)	7.88 ± 4.64	8.49 ± 4.98
Change from first to second look (mean ± sd)	–2.40 ± 3.66	–1.86 ± 3.35
LS mean for change[a] (95.2% CI)	**–2.22 (–2.83, –1.62)**	–1.60 (–2.24, –0.96)
p-value for change	<0.001***	<0.001***
Difference between LS means[b]	–0.62	
Se	0.31	
95.2% CI	(–1.24, –0.004)	
p-value for treatment	0.047	

a Estimated from an ANCOVA model with factors for treatment group and center and a covariate for first look score

b A negative difference favors ADEPT®

*** Statistically significant at the 0.1% level

Third primary effectiveness endpoint

	ADEPT®	LRS
Total number of patients	227	222
Number of sites with dense adhesions		
First look (mean ± sd)	6.17 ± 4.74	6.23 ± 5.26
Second look (mean ± sd) (n)	5.02 ± 4.60 (212)	5.25 ± 5.26 (208)
Change from first to second look (mean ± sd) (n)	–1.19 ± 3.43 (212)	–1.01 ± 3.24 (208)
p-value for change	<0.001	<0.001
Number of patients with fewer dense adhesions at second look	114 (50.2%)	109 (49.1%)
Odds ratio[a]	1.07	
95.2% CI for odds ratio	(0.72, 1.59)	
p-value for treatment	**0.73**	

a Estimated from a logistic regression model with factors for treatment group and center. A value >1 favors ADEPT®. The odds ratio (95.2% CI) using exact methods was 1.07 (0.71, 1.61).

Secondary effectiveness *(per protocol population)*

In all (10) secondary effectiveness variables, use of ADEPT® appeared to provide benefits beyond those provided by control, although not all to a statistically significant level. Both groups showed a reduction in adhesion burden, but this was consistently greater in the ADEPT® group. These secondary endpoints provide supportive evidence for the primary endpoints and have not been adjusted for multiplicity (see Tables 5 to 8). When a multiplicity adjustment is applied to the data, one secondary endpoint remains statistically significant in favor of ADEPT®: the subgroup of patients presenting with a primary diagnosis of infertility showed a statistically significant reduction in AFS score compared to control (p<0.05).

Table 5 : Pivotal Study Secondary Effectiveness Endpoints (PP) for Adhesions at Anatomical Sites

Endpoint / Variable	ADEPT® (n = 203)	LRS (n = 199)	p-value*
Incidence of sites with adhesions			
Change from 1st to 2nd look (mean ± s.d.)	–2.64 ± 3.66	–2.02 ± 3.19	0.039
% patients with reduction	76.4%	69.3%	0.121
Change from 1st to 2nd look excluding non-lysed sites (mean ± s.d.)	–2.64 ± 3.66	–2.02 ± 3.19	0.068
% patients with four or fewer sites with adhesions at 2nd look	32.0	28.1	0.510
Shift analysis – % patients with 2nd look incidence grouped into 4 categories	0: 4.9 1 – 4 27.1 5 – 9 36.0 ≥10 32.0	0: 4.5 1 – 4 23.6 5 – 9 31.7 ≥10 40.2	0.173
Severity of sites with adhesions			
% change from 1st to 2nd look per patient (mean ± s.d.)	–24.2 ± 45.2	–21.5 ± 41.0	0.415
% patients with reduction	72.9%	69.8%	0.446
Extent of sites with adhesions			
% change from 1st to 2nd look per patient (mean ± s.d.)	–26.9 ± 51.4	–21.8 ± 48.5	0.240
% patients with reduction	77.3%	69.8%	0.084
Modified AFS score			
Change from 1st to 2nd look (mean ± s.d.)	–0.67 ± 1.54	–0.48 ± 1.61	0.094
% patients with reduction	70.4%	69.8%	0.722

*** not adjusted for multiplicity.**

Table 6: Pivotal Study Secondary Effectiveness Endpoints (PP) for Subgroup of Patients with a Primary Diagnosis of Infertility

Endpoint / Variable	ADEPT® (n = 102)	LRS (n = 112)	p-value*
AFS score			
Change from 1st to 2nd look for patients with a primary diagnosis of infertility (mean ± s.d.)	–3.46 ± 6.77	–1.10 ± 6.36	0.011
% patients with reduction for patients with a primary diagnosis of infertility	52.9%	30.4%	0.001
Shift analysis – % patients with 2nd look scores grouped into 4 categories for patients with a primary diagnosis of infertility	min.: 68.6 mild: 10.8 mod.: 11.8 sev.: 8.8	min.: 59.8 mild: 13.4 mod.: 15.2 sev.: 11.6	0.041

*** not adjusted for multiplicity.**

Table 7: Pivotal Study Secondary Effectiveness Endpoints (PP) for Types of and Location of Adhesions

Endpoint / Variable	ADEPT® (n = 203)	LRS (n = 199)	p-value*
Reformed adhesions			
Number of sites with reformed adhesions (mean ± s.d.)	4.92 ± 3.91	5.11 ± 4.12	0.722
Number of sites without reformed adhesions (mean ± s.d.)	3.77 ± 2.72	3.32 ± 2.29	0.065
% patients with at least one	87.7%	86.9%	0.832
De novo adhesions			
Number of sites with at least one de novo adhesion (mean ± s.d.)	1.13 ± 1.85	1.29 ± 1.61	0.036
% patients free of de novo adhesions	52.7%	42.7%	0.029
Abdominal wall adhesions			
Change from 1st to 2nd look in number of sites (mean ± s.d.)	–1.17 ± 1.63	–0.94 ± 1.60	0.184
% patients with reduction from 1st to 2nd look in no. sites	65.5%	58.3%	0.129
Visceral adhesions			
Change from 1st to 2nd look in number of sites (mean ± s.d.)	–1.47 ± 2.62	–1.07 ± 2.22	0.046
% patients with reduction from 1st to 2nd look in no. sites	68.5%	63.3%	0.228

*** not adjusted for multiplicity.**

Table 8: Pivotal Study Secondary Effectiveness Endpoints (PP) for Subgroup of Patients with a Primary Diagnosis of Pelvic Pain

Endpoint / Variable	ADEPT® (n = 118)	LRS (n = 108)	p-value*
VAS score for pelvic pain			
Change from screening to 2nd look for patients with a primary diagnosis of pelvic pain (mean ± s.d.)	–35.8 ± 32.8	–30.8 ± 30.2	0.995

*** not adjusted for multiplicity.**

V. DIRECTIONS FOR USE

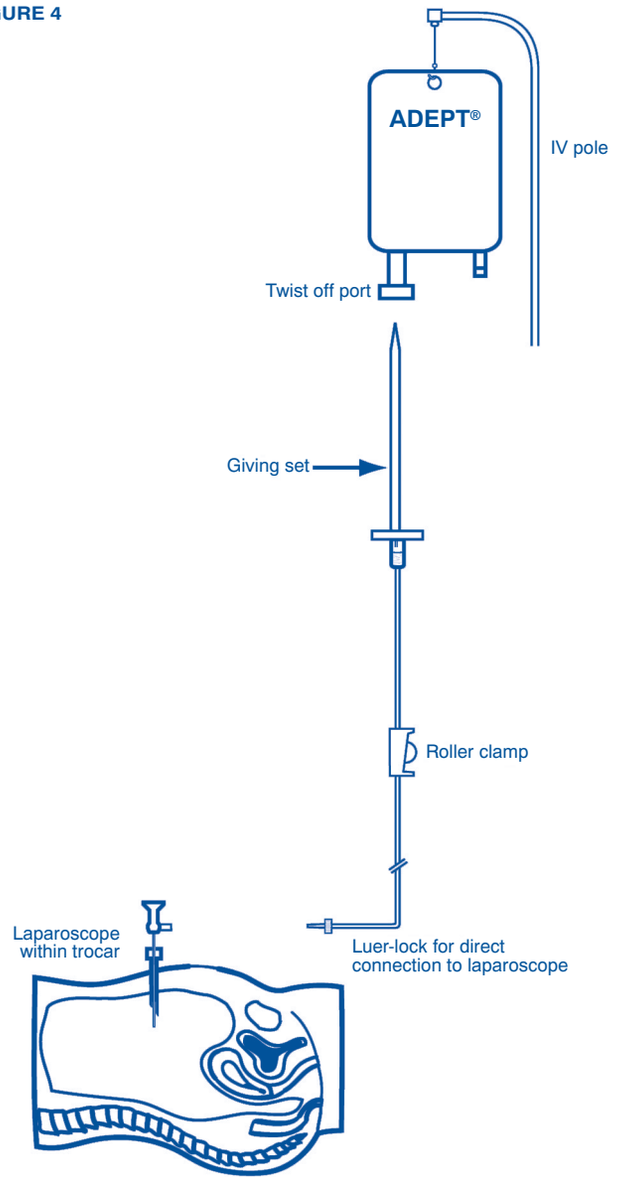
ADEPT® is administered directly into the peritoneal cavity during laparoscopic gynecological surgery, being used as an irrigant solution during the course of surgery. Once the surgeon has completed the surgical procedure(s), the cavity is aspirated of all remaining fluid. A final volume of 1 liter of ADEPT® is then introduced into the cavity before removal of the scope.

Using standard operating room technique:

1. ADEPT® should be warmed to approximately body temperature prior to use, using a device specifically intended for warming solutions in operating rooms.
2. Remove the outer wrap from the ADEPT® bag and hang the sterile bag of solution on an I.V. pole.
3. Remove the twist-off tab from the spike port and insert a giving set for connection to a laparoscope.
4. ADEPT® should be used intra-operatively as an irrigant solution, and as a post-operative instillate. The solution will flow through a giving set and through laparoscopes.
5. When used as an intra-operative irrigant solution, at least 100 mL of ADEPT® should be introduced to the cavity every 30 minutes.
6. Remove remaining fluid and exsufflate before introducing ADEPT®.
7. For the final instillation of ADEPT®, prior to removal of the laparoscope, one liter should be used. Direct the solution at the operative sites in the first instance, the remainder being distributed throughout the cavity.
8. Dispose of the bag and any unused portion of the solution following normal operating room biological hazard procedures.

SEE FIGURE 4

FIGURE 4



HOW SUPPLIED

ADEPT® is packaged in single use, flexible polyvinylchloride bags, fitted with connecting ports, containing 1.5 liters of solution. The product is presented sterile (by heating in an autoclave). The bags are packaged in cartons of 5 x 1.5 liters.

STORAGE

ADEPT® should not be stored above 30°C. Do not refrigerate or freeze.

ADEPT® may be kept in a warming device for up to 14 days, provided it is not removed and then replaced back in the warming device. At all other times, storage below 4°C or above 30°C is not recommended.

References:

1 Hosie K, Gilbert JA, Kerr D, Brown CB, Peers EM. Fluid dynamics in man of an intraperitoneal drug delivery solution: 4% icodextrin. Drug Deliv 2001; 8: 9 – 12

2 Moberly JB et al., Pharmacokinetics of Icodextrin in peritoneal dialysis patients. Kidney International 62, Suppl.81, 2002, S23 – S33.

3 Sutton C, Minelli L, Garcia E et al. Use of Icodextrin 4% solution in the reduction of adhesion formation after gynaecological surgery. Gynecological Surgery 2005; 2(4): 287 – 296.

4 Menzies D, Hidalgo M, Walz MD et al. Use of Icodextrin 4% solution in the prevention of adhesion formation following general surgery. Annals of the College of Surgeons of England 2006; 88 (4): 375 – 382.

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