# SUMMARY OF SAFETY AND EFFECTIVENESS DATA

## I. GENERAL INFORMATION

| | |
|---|---|
| ***Device Generic Name:*** | Absorbable adhesion barrier |
| ***Device Trade Name:*** | Adept® (4% Icodextrin) Adhesion Reduction Solution |
| ***Applicant's Name and Address:*** | Innovata plc<br>104a West Street<br>Farnham<br>Surrey<br>GU9 7EN<br>United Kingdom |
| ***U.S. Contact Name and Address:*** | New England Biomedical Research, Inc.<br>P.O. Box 809<br>96 West Main Street<br>NORTHBOROUGH MA 01532 |
| ***PMA Number:*** | P050011 |
| ***Date of Panel Recommendation:*** | March 27, 2006 |
| ***Date of Notice of Approval to Applicant:*** | July 28, 2006 |

## II. INDICATIONS 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.

## III. CONTRAINDICATIONS

Adept® is contraindicated:

- In patients with known or suspected allergy to cornstarch based polymers e.g., icodextrin, with maltose or isomaltose intolerance, or with glycogen storage disease;
- In the presence of frank infection (e.g., peritonitis) in the abdomino-pelvic 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; and

- 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.

## IV. WARNINGS AND PRECAUTIONS

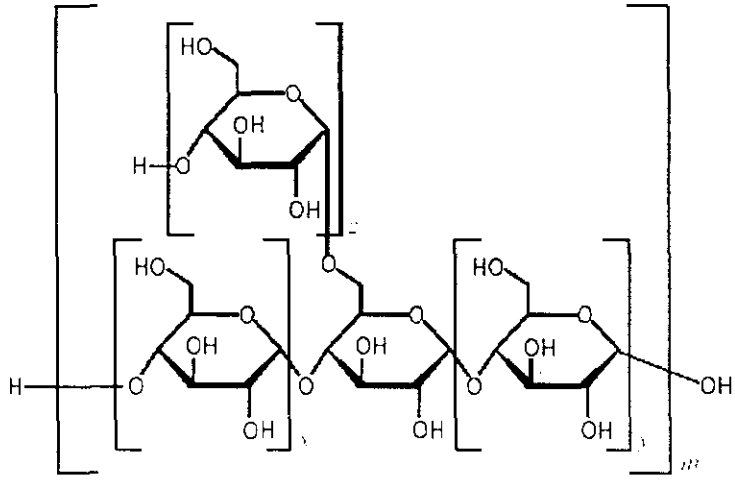
The Warnings and Precautions can be found in the Adept® device product labeling.

## V. DEVICE DESCRIPTION

### DEVICE DESCRIPTION

Adept® (4% Icodextrin) Adhesion Reduction Solution is a single use, sterile, clear, and colorless-to-pale yellow fluid for intraperitoneal administration containing Icodextrin at a concentration of 4% w/v in an electrolyte solution. Icodextrin is a corn starch-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. At least 85% or more of product has molecular weight between 1638 and 45,000 daltons. Additional specifications provide further uniformity of molecular weight distribution. The representative structural formula of Icodextrin is:

**Figure 1: Icodextrin**




Each 1 liter of solution contains:

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

Ionic composition (approximately) per liter:

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

Theoretical osmolarity 278 milliosmoles per liter

The viscosity of Adept® has been measured using the parallel plate method for shear rates up to 2000 $s^{-1}$. Adept® exhibits Newtonian behaviors over this range of shear rates; the viscosity is 1.2 cP at 20C and 0.93 cP at 37C.

The surface tension, measured using the DuNouy ring method, is 68 mN/m.

Adept® is packaged in flexible polyvinylchloride bags containing 1 L or 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®'s ability to draw limited amounts of fluid into the peritoneal cavity and to maintain a reservoir is achieved through the presence of molecular weight species of Icodextrin (>2000 MW) that are not rapidly absorbed across the peritoneal membrane. The persistence of this fluid reservoir is gradually decreased as Icodextrin and fluid are removed by lymphatic drainage and other clearance mechanisms.[2, 3]

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.[1]

### 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 7.5 % Icodextrin was absorbed from the peritoneal solution during a 12 hour dwell.[4]

### 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.[5] The rate of clearance of Icodextrin from the systemic circulation has been estimated to be equal to the glomerular filtration rate.

## VI. ALTERNATIVE PRACTICES OR PROCEDURES

Practices intended to minimize adhesion formation following gynecological laparoscopy include good surgical technique with attention to gentle and minimal tissue handling, meticulous hemostasis, avoidance of foreign particles (e.g., talc, lint), and use of an adjuvant such as crystalloid solutions. Crystalloid solutions are used but generally in volumes considerably less than 1 liter.

In the past twenty years, FDA has approved a number of post-operative adhesion barrier devices. They have been approved for open laparotomy gynecological procedures. None has been approved for laparoscopic gynecological procedures.

## VII. MARKETING HISTORY

Adept® (4% Icodextrin solution) was approved for intraperitoneal use as a medical device to reduce adhesions following abdominal surgery (laparoscopy and laparotomy) in the European Union (EU) member states in October 1999. It has been marketed in the United Kingdom since June 2000 and is now marketed in 28 countries.

European Union: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom.
Eastern Europe: Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovak Republic, Slovenia
Cyprus, Israel, Norway, and Switzerland

Adept® has not been withdrawn from the market for any reason related to the safety or effectiveness of the device.

Approximately 125,000 patients have been treated with Adept® up to March 2006. (see Section VIII.)

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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. Gynecologists and general surgeons were provided with forms to complete to enable them to report their experiences with the use of Adept® in the first 20-30 patients that they each treated. Data were collected between September 2000 and December 2003. A total of 4620 patients were enrolled in the ARIEL registry.



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Gynecological Surgery Registry[6]

The ARIEL gynecological registry included 2882 patients, (2069 laparoscopies; 813 laparotomies). Most surgeons rated the ease of use (viewing of surgical field, handling of tissues, overall satisfaction) of 4% Icodextrin solution as 'excellent' or 'good' and leakage from the surgical site as 'normal' or 'less than normal'. Abdominal discomfort was rated by surgeons as 'as expected' in 68% of laparoscopic patients and 67% of laparotomy patients and 'less than expected' in 24% of laparoscopies and 26% of laparotomies. Abdominal distension values were comparable. Adverse events occurred in 7.5% of laparoscopy patients and 13.9% of laparotomy patients.

General Surgery Registry[7]

The ARIEL general surgery registry included 1738 patients (269 laparoscopies, 1469 laparotomies,). Leakage of fluid from the surgical site did not appear to be affected by Icodextrin 4% solution and was classified as 'normal' or 'less than normal' in most patients. Overall satisfaction with ease of use was rated as 'good' or 'excellent' by the majority of surgeons. Patient acceptability was also good, with ratings of 'as expected' or 'less than expected' in most cases for both abdominal distension (91% laparoscopies, 90% laparotomies) and abdominal discomfort (93% laparoscopies, 91% laparotomies). Adverse events occurred in 16.7% of laparoscopy patients and 30.6% of laparotomy patients.

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 | Laparoscopy | Laparotomy | Not known | Laparoscopy | Laparotomy | Not known |
| Wound Complications[b] | 13 | 15 | 1 | 2 | 68 | 4 |
| Vulvar swelling | 7 | 1 | 3 | 0 | 1 | 0 |
| Failed anastamosis | 0 | 0 | 0 | 4 | 33 | 0 |
| Ileus | 3 | 2 | 1 | 4 | 46 | 1 |
| Pain | 15 | 10 | 2 | 4 | 9 | 0 |
| Pulmonary complication | 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[6] et al., and Menzies[7] 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 done 4-12 weeks after the initial procedure. In all three studies, the control device was Lactated Ringers Solution (LRS). Two pilot studies to obtain preliminary safety data enrolled a total of 99 subjects (59 Adept® treated, 40 LRS). The third US clinical trial of Adept® was the pivotal study, a randomized double-blind trial in which 449 subjects were treated, 227 with Adept® and 222 with LRS.

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 2L of Adept® vs. 1300mL 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 randomized double-blind, pivotal study, Adept® or LRS was used as an intra-operative irrigant (100mL every 30 minutes) and 1 L was instilled into the peritoneal cavity at the end of the procedure. Two hundred and twenty-one Adept® patients reported a total of 1065 events compared to 218 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.

## IX. SUMMARY OF PRECLINICAL STUDIES

### 1.1 Introduction

Icodextrin at 7.5% was originally developed by Innovata plc (formerly ML Laboratories plc) as an alternative to glucose as the osmotic agent in peritoneal dialysis (PD) fluid for patients with chronic renal failure. This peritoneal dialysis fluid is a 7.5% solution of Icodextrin in the same electrolyte vehicle as the 4% solution (Adept®). The toxicological investigations performed using 7.5% Icodextrin are therefore considered applicable to the proposed use of 4% Icodextrin for the reduction of post-surgical adhesions.

In PD, the route of administration is by daily intraperitoneal (IP) infusion and drainage of 1.5 – 2.5 liters of Icodextrin solution. This entails local exposure of the peritoneum and abdominal viscera, and systemic exposure, largely via passage into the lymphatics and by transperitoneal absorption, to Icodextrin itself and its physiological breakdown products. The exposure is continual on a daily basis.

Pharmacology and toxicity testing in animals were based on repeated IP instillation and removal of Icodextrin of various concentrations over a prolonged period. Single dose toxicity tests have also been performed.

In practice, experimentation was constrained by ethical concerns as well as practical considerations about the feasibility of regular IP instillation and drainage in experimental animals. The dosage administered was also sharply limited by the physiological consequences of instilling an increasingly concentrated (and viscous) solution into the abdomen. The conventional 'maximum tolerated dose' was considered to be attained by the disturbance of fluid and electrolyte balance produced by inward shift across the semi-permeable peritoneum into the pool of injected fluid in the peritoneal cavity. Accordingly, the multidose toxicity tests were designed to maximize the IP dose and exposure of the animals, while not subjecting them to unacceptable stress due to the procedure and its physiological effects, which would have represented an accentuation of its intended therapeutic purpose.

## 1.2 Non-Clinical Pharmacology

### *1.2.1 General (Safety) Pharmacodynamics*

The non-clinical general (safety) pharmacodynamic tests included:

- conventional experiments (blood pressure, cardiac activity respiration, response to IV noradrenaline) in the anesthetized and instrumented New Zealand White Rabbit injected with up to 1mg/kg IV Icodextrin;
- gastrointestinal transit time in the mouse following IP administration of 100mg/kg Icodextrin;
- organ bath studies testing up to 10% v/v Icodextrin on spontaneous motor activity of isolated guinea pig ileum and uterus, and on the responses of those tissues to autacoids (substances produced by various tissues in the body that cause slow contraction of smooth muscle).

All tests showed that Icodextrin is inert under clinically relevant circumstances.

### *1.2.2* Estimated Rate of Peritoneal and Systemic Clearance of Adept®.

Peritoneal and systemic clearance rates of Adept® have been estimated from data collected from PD patients receiving a single 2-liter dose of a 7.5% Icodextrin solution that was left in the peritoneal cavity for 12 hours.[4] The study consisted of 13 patients, nine of whom had residual renal function. Blood, dialysate, and urine samples collected after treatment were analyzed for the presence of Icodextrin and Icodextrin forms. Of the total dose of Icodextrin administered, approximately 40.1% was absorbed during the 12-hour dwell. The range of dose absorption from the peritoneum in these patients was found to be 24.2 to 63.8% of the administered Icodextrin dose. The investigators also determined that urinary excretion of Icodextrin and metabolites was directly related to residual renal function as shown by relative rates of creatinine clearance. Using this data, Innovata has estimated that the Icodextrin component of Adept® contained in 1 liter will be cleared from the peritoneum between 18 and 50 hours after administration, with estimated total body clearance between 31 to 63 hours.

### *1.2.3* Pharmacokinetics and Product Metabolism Studies in Animals

Since the metabolic pathways for Icodextrin-like structures are known and animals with normal renal function would not provide relevant information on the likely routes of elimination of Icodextrin in PD patients, conventional studies of kinetics and metabolism were not conducted. Studies concentrated on providing data for comparison of local and systemic exposure in test animals and in man.

Plasma and urine obtained from rats and dogs in the 28-day intraperitoneal toxicity studies were analyzed for Icodextrin and metabolites and the results are presented in Table 3 which includes data obtained from patients with and without renal function.

**Table 3: Comparison of Plasma Levels during Chronic Dosing With Icodextrin in Various Species**

| Species | Dose Details of Icodextrin | Sample Time (n) | Mean Plasma Levels of oligosaccharides (mg / ml) | | |
|---|---|---|---|---|---|
| | | | G2 | G3 - G10 | G>10 |
| Rat | 4.0 & 6.0 g / kg IP twice daily for 28 days | | None detected | | |
| Dog | 6.0 g / kg IP twice daily for 28 days (12 g / kg / day) | Pre-dose (8) | 0.02 | 0.02 | 0.10 |
| | | Day 1: 5h (8) | 0.11 | 0.52 | 0.17 |
| | | Day 1: 24 h (8) | 0.02 | 0.22 | 0.13 |
| | | Day 21: 5 h (8) | 0.05 | 0.33 | 0.18 |
| | | Day 21: 24 h (8) | 0.02 | 0.24 | 0.16 |
| | | Day 28: 5h (8) | 0.03 | 0.28 | 0.14 |
| | | Day 28: 24 h (8) | 0.02 | 0.26 | 0.16 |
| Man – PD patients[2)] | 150 g once daily IP for 6 months (2.14 g/kg/day) | Pre-dose (91) | 0.04 | 0.02 | 0.29 |
| | | 1 month (80) | 1.20 | 1.84 | 1.83 |
| | | 3 months (72) | 1.00 | 1.67 | 1.73 |
| | | 6 months (53) | 1.06 | 1.76 | 1.84 |

The data demonstrate the brief systemic exposure of the rat and the somewhat longer period in the dog, although both are less than in man.

It is apparent that systemic exposure of experimental animals to Icodextrin and its principal breakdown products in animals is limited relative to that of man. Also the exposure to these substances of patients receiving IP treatment with 4% Icodextrin is considerably less than in patients being treated with 7.5% Icodextrin for PD. Knowledge of the safety and tolerability of Icodextrin in the latter subjects is therefore validated as the best possible guide to the safety and acceptability of 4% Icodextrin IP.

## 1.3 Toxicology

### 1.3.1 *Single Dose Toxicity Tests*

Acute IV and IP studies have been conducted in mice and rats and have demonstrated no effects at doses up to 2000mg/kg.

### 1.3.2 *Repeated Dose Toxicity Studies*

Twenty-eight day studies were conducted in rats and dogs involving twice daily IP administration of up to 30mL/kg 20% Icodextrin solution (up to 12g/kg/day). In the rat the treatment was administered by twice daily IP injections but in the dog a catheter was surgically implanted and the solution instilled into and removed from the peritoneal cavity twice daily. No target organ or tissue toxicity was produced. There was no evidence of storage of the dextrin in local or distant tissues. The overall pattern of changes in both species was of relatively slight but predicted effects on fluid and electrolyte balance, related

to the duration of effective exposure to Icodextrin, and of secondary adrenal cortical (zona glomerulosa) hyperplasia and mild hyperglycemia in the dog. The differences between the species are considered to result from differences in the duration and magnitude of the physiological disturbances produced by the treatments, which is due to differences in the excretion and metabolism of Icodextrin.

All the changes had largely or completely disappeared after a 14-day recovery period.

1.3.3 *Mutagenicity*

Mutagenicity testing comprised:

- An Ames test at up to 10,000μg Icodextrin/plate.
- An *in vitro* cytogenetic test in Chinese hamster ovary (CHO) cells at up to 200mg/mL Icodextrin, in the presence and absence of S9 microsomes.
- A mouse micronucleus test involving mice of both sexes given up to 6g/kg Icodextrin IP.

Negative results were obtained in all three tests, indicating that Icodextrin does not possess chemical structures known to be or found to be capable of being metabolized to mutagenic electrophilic groups.

1.3.4 *Reproductive Toxicity*

In a combined study of the effects on fertility and embryo-fetal toxicity (segment I/II) in the rat, males were dosed for 29 days before pairing, throughout pairing and until termination and females were treated for 15 days prior to pairing through to day 17 of gestation. The results showed that the top female and male doses of 10mL/kg/day (approximately 0.6g/day) and 20mL/kg/day (approximately 2g/day) IP, respectively of 20% Icodextrin solution had no adverse effects on general condition, mating performance, fertility and embryo-fetal development. These dose volumes were considered to be the maximum which would be practical under the conditions of the study.

1.3.5 *Local Toxicity Studies*

1.3.5.1 *Irritancy*

Specific studies have not been conducted, but there is evidence from other studies that 20% Icodextrin appears to be a reasonably non-irritating solution for IP use. Clinical and necropsy observations in the acute toxicity tests did not show any features of local irritation. These results were reinforced in the 28-day IP tests in the rat and dog in which histological examination of the serosal and visceral peritoneum was conducted.

In addition, in the 28-day experiment in the dog, residual peritoneal fluid was sometimes obtained *in vivo* and at autopsy. It did show a variable, low leukocyte count and protein content in most instances, but this was often exceeded by the values in fluid from animals receiving 5% glucose IP. The latter might have been anticipated in view of the known irritancy (in man) of 5% glucose.

1.3.5.2 *Peritoneal Macrophages and Polymorphonuclear Leukocytes (PMN)*

The peritoneal cavity is normally sterile. It is assumed that sterility is maintained in part by the cidal activities of local and immigrating macrophages and PMNs. Means to examine the

numbers and activities of such cells have not been developed in a standardized way, but some screening experiments have been conducted using short-term cultures of human peripheral neutrophils and peritoneal macrophages[8] and in independent experiments on THP-1 human monocyte cells. The results indicate that although Icodextrin may have had an effect in *in vitro* tests on certain leukocyte functions, their relevance to *in vivo* host defenses is unknown. In addition, there was no clinical evidence of reduction in peritoneal defenses.

### 1.3.6 *Effect on Peritoneal Metastases*

A rat adhesion model and rat tumor adhesion and growth model (using IP injection of the colon carcinoma cell line CC531) were used in a study to evaluate the adhesion preventing properties of 7.5% Icodextrin and its effects on peritoneal metastasis compared to placebo (Roswell Park Memorial Institute (RPMI-1640) media) and untreated (surgical) controls[9]. Perioperative intra-abdominal treatment with 7.5% Icodextrin caused a 51% reduction in postoperative adhesion formation ($p < 0.001$) of rats whose peritoneal cavity was traumatized compared to untreated control. Perioperative intra-abdominal treatment with 7.5% Icodextrin did not affect intraperitoneal tumor cell adhesion and growth of free intra-abdominal tumor cells in rats with this model of severe peritoneal trauma.

### 1.3.7 *Conclusions of Toxicology Studies*

The important points for clinical consideration, based on the non-clinical tests, are that, following IP doses of up to 12g/kg/day for 28 days in the rat and dog:

- No target organ or tissue for toxicity has been identified, but the chemical nature and physiological properties of Icodextrin do not suggest that conventional target organ toxicity should be anticipated.

- There was no evidence of local lesions in the peritoneum and its associated blood vessels and lymphatics due to exposure to the Icodextrin instilled IP, nor was there any sign of storage of the Icodextrin in local or distant tissues, including lymphoid organs and major viscera.

- Hyperplasia of the zona glomerulosa in the dog adrenals was seen and was considered part of a response to the disturbance of fluid and electrolyte balance produced in the toxicity test. Both of these effects in the dog were reversible.

## 2.1 Preclinical Effectiveness Studies

Four percent Icodextrin solution has been assessed for its potential to prevent/reduce the formation of adhesions in the rabbit double uterine horn and rabbit sidewall formation and reformation models.

### *2.1.1 Rabbit Double Uterine Horn Model*

A series of studies[10] has shown that 4% Icodextrin solution used as a lavage during surgery and as an instillate (50mL) post-operatively reduced adhesion formation in the rabbit double uterine horn model, compared to surgical controls and placebo solution, with no inflammation or excess fluid at necropsy.

A further study has been conducted in the same animal model to compare Adept® and Intergel (0.5% ferric hyaluronate gel) against surgical controls, in a blinded manner. In this study, Adept® was administered both peri- and postoperatively while Intergel was administered postoperatively only (to reflect the intended clinical usage). At the end of surgery, 50mL Adept®, 15mL of Intergel or no treatment (surgical controls) were administered. The results have shown fewer adhesions in animals treated with Adept® and Intergel.

*2.1.2 Rabbit Sidewall Model*

An additional study[9] has shown that the instillation of 50mL 4% Icodextrin solution at the end of initial surgery, or after further surgery for adhesiolysis, reduced the incidence and extent of adhesion formation compared to surgical controls in the rabbit sidewall formation and reformation model of adhesions between the sidewall and cecum and bowel. Histopathologic evaluation of the site of the sidewall injury showed no excess inflammation and a normal healing process comparable to controls at necropsy.

## *2.2 Additional Safety Studies*

*2.2.1 Effects on Infection Potentiation*

The effect of administration of 4% Icodextrin on abscess formation following intraperitoneal infection in rats has been evaluated in the Onderdonk animal model for bacterial peritonitis[9]. A bacterial inoculum sufficient to cause death in either 40-60% or 0-20% of rats was placed in the abdomen of groups of 15 rats which received additionally 4% Icodextrin solution, Lactated Ringer's Solution (LRS) or no further treatment (surgical control) intraperitoneally at the end of surgery. The rats were observed until day 11 post-surgery when they were sacrificed. No increased risk was observed for the use of 4% Icodextrin intraperitoneally in an infected abdomen based upon overall survival, abscess score or incidence of abscesses in this animal model.

*2.2.2 Anastomotic Healing*

A study to evaluate the effect of Adept® used both as a perioperative lavage and post- operative instillate, on the healing of a bowel anastomotic site and a laparotomy incision was evaluated in a rabbit model. The strength or integrity of these healing sites in animals treated with Adept® was compared in a blinded manner to healing in animals treated with LRS or surgery only. In the treated groups, the test and control materials were used intraoperatively and left postoperatively in the rabbit abdominal cavity after re-anastomosis. The surgical group underwent re-anastomosis surgery only. No statistical differences were noted between groups for tissues evaluated for adhesions, abscess, bursting and tear strength. Histological assessment of the bowel and abdominal muscle repair sites for inflammation, fibroblast growth, blood vessel formation and collagen maturity did not reveal any statistically significant differences between the groups.

*2.2.3 Hemolysis*

Icodextrin was found to be non-hemolytic in a direct contact hemolysis test (ISO 10993-4).

## X. SUMMARY OF CLINICAL STUDIES

Adept® has been studied in the US in two pilot studies and one 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 in 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 US. 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 an 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 adhesions 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**

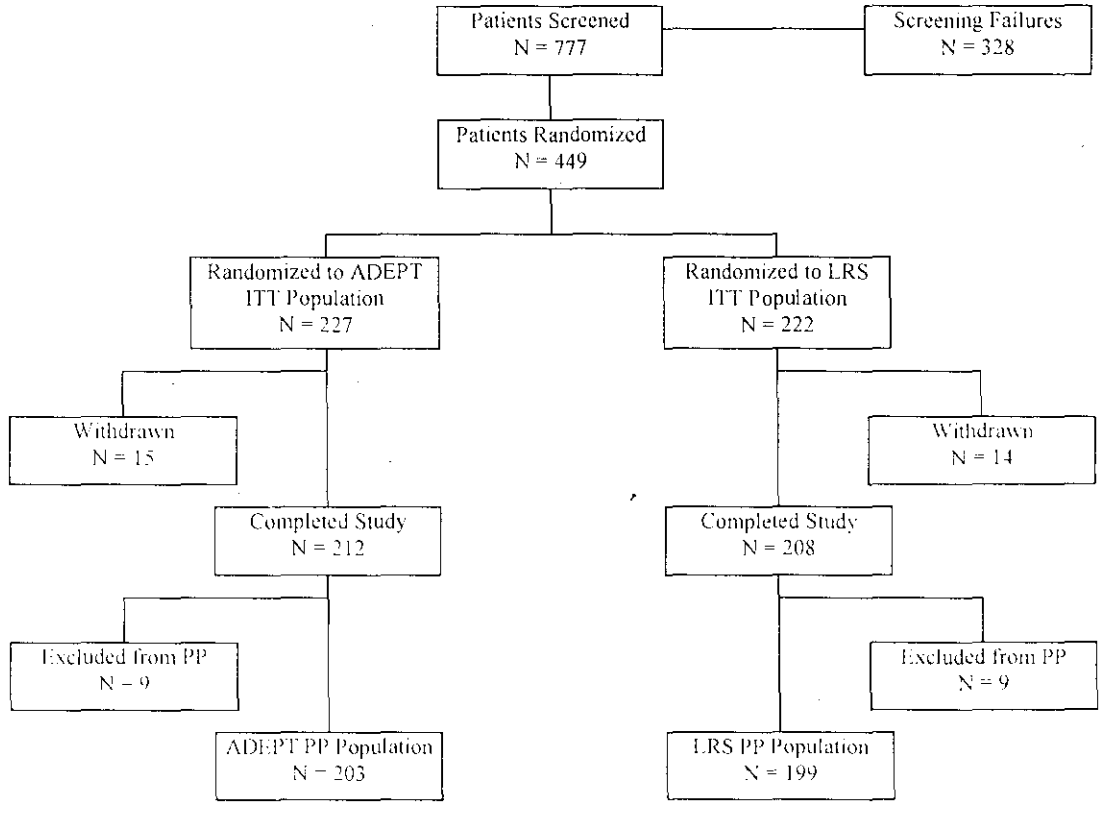


**Table 4: Pivotal Study Demographics and Baseline Data, ITT**

| | | ADEPT® | LRS |
|---|---|---|---|
| # 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 n(%): | Caucasian | 160 (70.5%) | 144 (64.9%) |
| | 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 (%)** | | | |
| # of patients with resolved medical conditions | | 192 (84.6%) | 191 (86.0%) |
| # 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 4 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). 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) (Figure 3 and 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 (Figure 4). Data is presented as intent-to-treat (ITT). (see Figures 3 and 4.)

**Figure 3: 1st Co-Primary Endpoint, percentage of patients achieving 'success', ITT population**

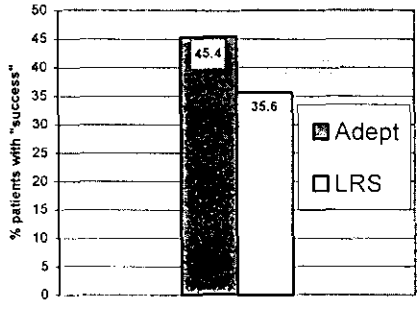
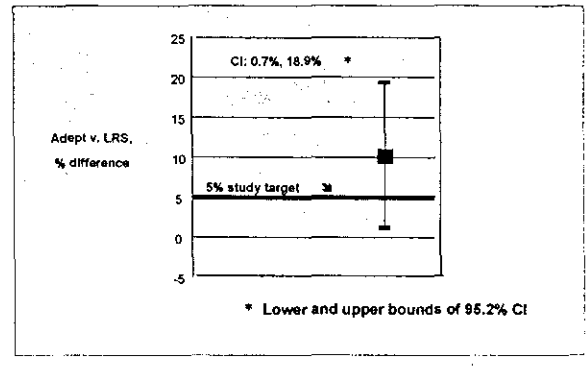



**Figure 4: 1st Co-Primary Endpoint, difference in 'success' rate between Adept and LRS, ITT population**




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 5). There was no statistically significant difference between treatments (p=0.73).

## Table 5: Pivotal Study Primary Effectiveness Endpoints, ITT 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* (PP) population**

Secondary endpoints were evaluated on a *per protocol* basis, i.e., excluding protocol violations. 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.

Tables 6-9 show that these secondary endpoints provide supportive evidence for the primary endpoints. However, these numbers have not been adjusted for multiplicity. 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 the control ($p<0.05$).

**Table 6: 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-lyzed 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<br>1-4 27.1<br>5-9 36.0<br>≥10 32.0 | 0: 4.5<br>1-4 23.6<br>5-9 31.7<br>≥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 7: 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 | minimal: 68.6<br>mild: 10.8<br>moderate: 11.8<br>severe: 8.8 | minimal: 59.8<br>mild: 13.4<br>moderate: 15.2<br>severe: 11.6 | 0.041 |

* not adjusted for multiplicity.

**Table 8: Pivotal Study Secondary Effectiveness Endpoints (PP) for 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 9: 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.

## XI. CONCLUSIONS DRAWN FROM THE STUDIES

Adept® has been evaluated in three randomized, controlled clinical studies (two pilot and one pivotal study). A total of 286 subjects have been treated with Adept® and 262 subjects have been treated with LRS. In the randomized, double-blinded pivotal clinical trial, 45% of subjects treated with one liter of Adept® had a decrease of ≥3 sites with adhesions compared to 35% of subjects treated with LRS (p=0.001). On average, adhesions did not become worse between first- and second-look laparoscopy even among subjects who did not meet the subject-level study definition of success of ≥3 fewer sites with adhesions. Also, for both Adept® and LRS, sites with dense adhesions decreased on average by at least one site.

Strictly speaking, the study was not a success because the statistical hypothesis for only one of the 3 co-primary endpoints was met. This was for the endpoint that looked at whether subjects got worse. For one of the two "failed" hypotheses, Adept® did perform statistically significantly better than LRS, however the lower bound on the 95% CI did not meet the threshold set in advance by the Food and Drug Administration (FDA). Regarding the other "failed" hypothesis, both Adept® and LRS had a statistically significant decrease in sites with dense adhesions, however Adept® was not superior to LRS for that endpoint. In summary, the statistical hypothesis was met for only one of three co-primary endpoints, but Adept® performed better than LRS for two of the outcomes measured, and performed as well as LRS for the third outcome.

The Pivotal Clinical Trial also had ten secondary endpoints, all of which showed at least a trend in favor of Adept® over LRS. Only one of the secondary endpoints was statistically significant in favor of Adept® after a multiplicity adjustment was applied to the data. That endpoint was improvement in the AFS adhesion score among subjects whose primary diagnosis included infertility.

The safety of Adept® compared to LRS was supported by the finding of no increase in serious device-related adverse events. The most serious adverse events in both arms of the study were two cases of prolonged or unplanned hospitalization due to urinary retention and/or pain. All subjects were managed conservatively and discharged within 24 hours. The most common device-related adverse event in the Adept® subjects is edema in vulvar tissues. This is a known unpleasant but non-serious side effect of Adept® which was also observed in the pilot studies and occurs at a rate of 5-6%. Most cases resolved within one week without intervention.

FDA also reviewed post-market clinical data on the safety of Adept® 4% Icodextrin from the European ARIEL Registry. This Registry solicited data from approximately 4600 subjects who had undergone gynecological or general surgical procedures over a three-year period. Of these, approximately 2900 were gynecology patients (72% laparoscopy) and 1700 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.

Because the ARIEL data were registry data and not clinical trial data, the relationship of the adverse events to use of Adept® is unknown. The most commonly reported adverse event in the ARIEL Registry was wound complication. The most serious adverse event associated with Adept® was failed intestinal anastamosis and resulting morbidity. Vulvar edema was also reported. FDA review of the ARIEL data as well as the US Clinical Trials data resulted in Contraindications for use of Adept® following laparotomy incision (due to wound complications) and following surgical procedures involving the intestine. The observation of wound complication also led to a recommendation that surgeons close the fascia at the laparoscopic trocar sites to prevent leaking of Adept® into the subcutaneous tissue at those sites.

Finally, the CDRH Adept® review team collaborated with reviewers in FDA's Center for Drug Evaluation and Research (CDER) to review approximately 280 adverse event reports submitted to FDA for Extraneal™ 7.5% Icodextrin Peritoneal Dialysis solution. Extraneal™ differs from Adept® in that it is a more concentrated form of Icodextrin, it is administered in larger volumes compared to Adept®, it is removed following a dwell times of 8 to 16 hours, and it is prescribed for a patient population with serious illnesses including renal failure. Despite these differences, FDA felt that review of Adept® required knowledge of adverse events associated with Extraneal™, such as sterile peritonitis. FDA's review concluded that all risks associated with Extraneal™ were reflected in the existing drug labeling for that product. Sterile peritonitis is reported rarely, although a spike in reports during 2001-2002 caused the manufacturer to conduct a voluntary recall of selected lots of Extraneal™. After procedures were instituted to limit the level of peptidoglycan during manufacturing, reports of sterile peritonitis returned to baseline. The risk of other adverse events noted with Extraneal™ (such as the possibility of falsely elevated blood sugar readings in diabetic patients who use non-glucose specific methods for monitoring sugar levels) were added to labeling for Adept® to ensure that its labeling is comprehensive.

On the basis of FDA's review of the Adept® US clinical trials, review of post-marketing registry data from outside of the US and safety data reported to FDA on Icodextrin 7.5%, FDA has concluded that Adept® is safe and effective for adhesion reduction following gynecologic laparoscopic surgical procedures involving adhesiolysis when used according to product labeling.

## XII. PANEL RECOMMENDATIONS

On March 27, 2006, FDA's Obstetrics and Gynecology Devices Panel considered the PMA for the Adept® (4% Icodextrin) Adhesion Reduction Solution. The panel acknowledged that the study failed to achieve its mark for two of the three co-primary study endpoints in the pivotal clinical study. However, the panel also noted the relatively safe risk profile for this product, including data from outside the US. The panel unanimously recommended approval of the PMA for the Adept® product, conditional upon a number of changes to the professional labeling.

The Panel's recommendation included revision of Adept® (4% Icodextrin) Adhesion Reduction Solution's indication for use to be modified by limiting it use to laparoscopic surgery patient undergoing adhesiolysis. In addition, the Panel recommended revisions to existing precautions, the definition of success for the first co-primary endpoint, and to the directions for use. The Panel also suggested that the labeling present all secondary endpoints.

## XIII. CDRH DECISION

CDRH concurred with the Panel's recommendation, and issued a letter to Innovata plc, dated May 30, 2006, advising that its PMA was approvable subject to labeling revisions regarding adverse events from post-marketing experience outside of the US and subject to post-approval reporting requirements related to adverse events.

All conditions of the approval have been resolved through written communication with Innovata plc. CDRH has determined the Adept® (4% Icodextrin) Adhesion Reduction Solution to be safe and effective for use as an adjunct to good surgical technique for the reduction of post-surgical adhesions in patients undergoing gynecologic laparoscopic adhesiolysis.

The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

FDA issued an approval order on July 28, 2006.

## XIV. APPROVAL SPECIFICATIONS

Directions for use: See the Device Labeling.

Hazards to Health from Use of the Device: See Indication, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.

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