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**CORRESPONDENCE - 220 pages**

**1**

**PREMARKET APPROVAL APPLICATION**

**SUBMISSION TO FDA**

**FOR**

**ADEPT™**

**SPONSOR PANEL PACK**

**P050011**

**VOLUME 1 SECTIONS 1 - 4**

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**February 2006**

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## 1. DRAFT LABELLING

The draft labelling is provided overleaf.

**ADEPT®****(4% ICODEXTRIN SOLUTION)****ADHESION REDUCTION SOLUTION**

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

**MANUFACTURED FOR:**

Innovata plc  
104A West Street  
Farnham  
Surrey  
GU9 7EN  
United Kingdom

**DESCRIPTION**

ADEPT Adhesion Reduction Solution is a single use, sterile, clear, colourless to pale yellow fluid for intraperitoneal administration containing icodextrin (an  $\alpha$ -1,4-linked starch-derived glucose polymer) at a concentration of 4% w/v in an electrolyte solution.

Each 1 liter of solution contains:

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

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 liter or 1.5 liters of solution. When stored at temperatures below 30°C ADEPT has a shelf life of 24 months. ADEPT should not be refrigerated or frozen.

## INDICATIONS

ADEPT Adhesion Reduction Solution is intended for use as an adjunct to good surgical technique for the reduction of post-surgical adhesions in patients undergoing gynecological laparoscopic surgery which may include adhesiolysis. ADEPT should be used as both an intra-operative irrigant and post-operative instillate during the surgery.

## ACTIONS

Icodextrin, as a glucose polymer, is similar in structure to carbohydrates which occur physiologically. When administered intraperitoneally as a 4% solution, it is capable of maintaining a reservoir of fluid within the peritoneal cavity.

When given intraperitoneally, the polymer is not metabolised significantly in the peritoneum but is slowly transferred into the systemic circulation by peritoneal lymphatic drainage over a period of 2 to 3 days. Icodextrin in the systemic circulation is eliminated both by rapid metabolism by serum amylase to low molecular weight fragments and by renal excretion. Clearance of icodextrin from the systemic circulation has been estimated to be equal to glomerular filtration rate.

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

## CONTRAINDICATIONS

ADEPT should not be used in patients with a known allergy to starch based polymers or in patients with maltose or isomaltose intolerance.

## WARNINGS

ADEPT must be used as directed by a physician. It must not be used unless the solution is clear and the container undamaged.

Any unused portion of solution should be discarded. ADEPT is not to be used for intravenous infusion.

## PRECAUTIONS

The safety and effectiveness of ADEPT in children (patients less than 18 years of age) has not been evaluated.

The safety and effectiveness of ADEPT in pregnancy has not been evaluated. No clinical studies have been conducted in pregnant women although some women have become pregnant within the first month after exposure to ADEPT. Therefore, this product is not recommended for use during pregnancy and avoidance of conception should be considered during the first complete menstrual cycle after use of ADEPT.

Foreign body reactions may occur with ADEPT, as with any implanted material.

The safety and effectiveness of ADEPT has not been evaluated in clinical studies in the presence of frank infections in the abdominopelvic cavity.

The safety of ADEPT has not been established after unintentional enterotomy or bowel perforation

Late onset (up to 14 days after instillation of device) severe abdominal-pelvic pain may present as a self limited symptom associated with normal temperature, normal WBC, present bowel sounds, and absence of peritoneal rigidity. This should be distinguished from peritoneal cavity infection, perforated bowel or other viscous, intraperitoneal bleeding, or other postoperative complications.

Pleural effusion may present as a self limited symptom which should resolve without intervention.

It is intended that 1 liter of ADEPT is instilled into the peritoneal cavity at the end of surgery. In clinical studies of ADEPT up to 2 liters of solution have been instilled (not adjusted for body weight). The safety of larger (than 2 liters) volumes and the efficacy of smaller (than 1 liter) volumes have not been established.

## ADVERSE EVENTS

ADEPT has been studied in three randomized, controlled US clinical trials involving a total of 548 patients undergoing gynecological laparoscopic surgery. Two safety studies enrolled a total of 99 (59 ADEPT treated, 40 control) patients and the third, a double-blind pivotal study, enrolled 449 (227 ADEPT treated, 222 control) patients.

No significant differences were observed in the incidence of adverse events, serious or non-serious, comparing 286 ADEPT treated and 262 control (Lactated Ringer's solution) patients over the period between the initial and second-look surgeries; ie up to 12 and 8 weeks in the pilot and pivotal studies, respectively.

In general, adverse events reported in the clinical studies were those typically expected following surgery and were generally mild to moderate and resolved either spontaneously or with routine post-operative care/medication.

In the double-blind, pivotal study, the treatment groups were balanced with respect to the number of patients reporting adverse events overall, serious adverse events, and in terms

of timing of events in relation to surgery. Overall, 221 (97.4%) ADEPT patients reported a total of 1065 events compared to 218 (98.2%) control patients who reported 1047 events.

In the pivotal study, the most common reported event was post-procedural pain followed by headache. Other prevalent events included nausea, post procedural discharge, dysmenorrhea, constipation, and pelvic pain. Less common events included arthralgia, flatulence, urinary tract infection, abdominal pain, dysuria, nasopharyngitis, vaginal bleeding. (The vaginal bleeding events were not considered to be related to ADEPT or control and none was considered to be severe.). Table 1 presents adverse events reported in  $\geq 5\%$  of patients (regardless of causality) in the pivotal trial.

**Table 1: 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 Population**

	ADEPT		Control	
	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
Post procedural discharge	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
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) adverse events reported as treatment related were post procedural discharge (12.8% ADEPT; 10.4% control), post procedural pain (3.5% ADEPT; 3.1% control), abdominal distension (3.5% ADEPT; 1.8% control), and labia enlarged/vaginal swelling (3.5% ADEPT; 0.0% control). Apart from the post procedural pain which is an expected event following surgery, these events are probably the result of the presence of fluid in the peritoneal cavity. Labial edema is a recognised event associated with the use of fluids for irrigation and instillation in laparoscopic surgery. The edema results from fluid entering the labia from the peritoneal cavity via the Canal of Nuck or other fascial defects or planes. The fluid is typically resorbed spontaneously within a few days which is facilitated by bed rest and usually does not require drainage. However, if persistence of labial edema or evidence of secondary infection develops, then intervention may be necessary.

Other adverse events reported as related in the ADEPT-treated group included:  
*reported at an incidence of <2%:* abdominal pain, nausea, edema (including generalised and peripheral), and dysuria

*reported at an incidence of <1%:* constipation, flatulence, application site swelling, chest pain, post operative fever, arthralgia, back pain, insomnia, bladder discomfort, pollakiuria, pelvic pain, pruritis generalised, and rash.

There have been rare (0.02%) reports of hypersensitivity reactions in patients treated with ADEPT.

It is possible that the patient may feel bloated for a short time, indicating the presence of fluid in the abdomen.

## CLINICAL STUDIES

ADEPT has been studied in the USA in two pilot studies and one double-blind, pivotal study in female patients undergoing gynecological laparoscopic surgery with a planned second-look laparoscopy. The studies were conducted to evaluate the safety and efficacy of the device as an adjunct to good surgical technique in the reduction of post-surgical adhesions in comparison to Lactated Ringer's Solution (LRS). ADEPT or LRS was used as an intra-operative irrigant (100 mls every 30 minutes) in all studies. In the pilot studies, 1 liter of ADEPT was instilled into the peritoneal cavity at the end of the surgical procedure in the first study, and up to 2 liters in the second study, whilst the volume of LRS instilled was dependant upon the normal practice at the study centre. In the pivotal study, 1 liter of ADEPT or LRS was instilled in a double-blind manner at the end of the procedure. In all studies, the incidence, extent and severity of adhesions were assessed at 23 prospectively determined anatomical sites, using prospectively established scales for extent and severity, before adhesiolysis at baseline surgery and at second-look laparoscopy. Safety was evaluated based on adverse events recorded throughout the study, changes in clinical laboratory tests, post-operative recovery (changes in concomitant medication), and on gross adhesion evaluation at second-look.

The pilot studies were comparative, open-label, randomized, multicentre studies. The first study enrolled 62 patients (34 ADEPT-treated, 28 control) and the second enrolled 37 patients (25 ADEPT-treated, 12 control). Both studies showed that ADEPT has a similar safety profile to control when used as an intra-operative irrigant and post-operative instillate (up to 2 liters) in laparoscopic gynecological adhesiolysis procedures.

### PIVOTAL STUDY

The pivotal study was a comparative, double-blind, randomized, multicentre study. 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 to 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. Table 2 presents the accounting, demographics, and baseline data for the study.

Table 2: Pivotal Study Accounting, Demographics and Baseline Data

	ADEPT	Control	Overall
No. patients randomized (Intention to Treat)	227	222	449
No. patients completed study (ie with second-look)	212	208	220
No. patients per protocol (Per Protocol)	203	199	402
Demographics:			
Age (yr) (mean±sd)	32.6±5.9	32.3±5.7	32.4±5.8
Height (in) (mean±sd) (n)	64.7±2.7 (225)	64.2±2.8 (221)	64.4±2.8 (446)
Weight (lb) (mean±sd) (n)	153.2±36.9 (225)	152.0±35.0 (220)	152.6±36.0 (445)
Race (n: %):			
Caucasian	160 (70.5)	144 (64.9)	304 (67.7)
East Asian	3 (1.3)	7 (3.2)	10 (2.2)
Afro-Caribbean*	32 (14.1)	32 (14.4)	64 (14.3)
Hispanic	24 (10.6)	35 (15.8)	59 (13.1)
Oriental	3 (1.3)	1 (0.5)	4 (0.9)
Other	5 (2.2)	3 (1.4)	8 (1.8)
No. of Sites with Adhesions at Baseline (mean±sd) (Intention to Treat)	10.27±4.26	10.34±4.39	10.31±4.32
Baseline AFS score for infertility subgroup (mean±sd) (Per Protocol)	8.98±9.86	8.20±9.88	8.57±9.86
Baseline mAFS score (mean±sd) (Per Protocol)	2.71±2.47	2.81±2.93	2.76±2.70
Operative Time (mins) (median) (Intention to Treat)	85.0	88.0	88.0
Days between first and second look surgery (Intention to Treat)	39.9±10.3	39.9±10.7	39.9±10.5

\* CRF term

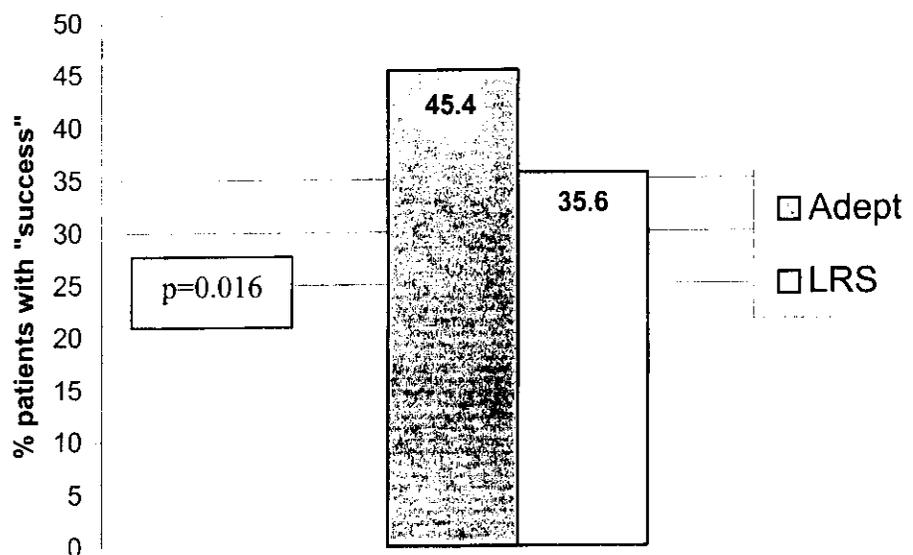
For efficacy, the primary variable was incidence of adhesions. Secondary variables included (incidence), extent, and severity of adhesions, American Fertility Society (AFS) score, modified American Fertility Society (mAFS) score, reformed and de novo adhesions, abdominal wall adhesions, visceral adhesions, and pain VAS score for patients with a primary diagnosis of pelvic pain.

The first primary efficacy endpoint was "success rate" which was defined as the proportion of patients for whom the number of sites with adhesions decreased by at least the larger of three sites or 30% of the number of sites lyzed.

Primary efficacy (Intention to Treat population)

1. A significantly greater percentage of patients, 45.4%, in the ADEPT group was defined as a “clinical success” compared to 35.6% in the control group ( $p=0.016$ , two-tailed test;  $p=0.008$ , one-tailed test) (Figure 1 and Table 3).

**Figure 1: Pivotal Study First primary efficacy endpoint (Percentage of patients achieving ‘success’) – Intention to Treat population**



**Table 3: Pivotal Study First primary efficacy endpoint – Intention to Treat Population**

	ADEPT	Control
Total number of patients	227	222
<b>Success<sup>a</sup></b>		
Number reporting	103 (45.4%)	79 (35.6%)
Difference in % of patients with success		9.8
se		4.6
<b>95.2 CI for % of patients with success</b>		<b>0.7, 18.9</b>
Odds ratio <sup>b</sup>		1.64
95.2% CI for odds ratio		1.09, 2.46
p-value for treatment		0.016 * (0.008) *
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 lyzed	
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 (statistically significant at the 2.4% level, one-tailed)	

2. 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 interval was less than zero in the ADEPT-treated patients (-2.83 to -1.62). In addition there was a significantly greater reduction in the number of sites with adhesions in the ADEPT treated patients compared with the control group ( $p = 0.047$ , two-tailed test;  $p = 0.023$ , one-tailed test) (Table 4).

**Table 4: Pivotal Study Second primary efficacy endpoint – Intention to Treat population**

	ADEPT	Control
Total number of patients	227	222
<b>Number of sites with adhesions</b>		
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
<b>LS mean for change<sup>a</sup> (95.2% CI)</b>	<b>-2.22 (-2.83, -1.62)</b>	<b>-1.60 (-2.24, -0.96)</b>
p-value for change	<0.001 ***	<0.001 ***
Difference between LS means <sup>b</sup>		-0.62
se		0.31
95.2% CI		-1.24, -0.004
<b>p-value for treatment</b>		<b>0.047 * (0.023) *</b>
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 4.8% level, two-tailed (statistically significant at the 2.4% level, one-tailed)	
***	Statistically significant at the 0.1% level	

3. In the ADEPT group, 50% of patients had fewer sites with dense adhesions at second look ( $p < 0.001$ ); in the control group, the figure was similar (49%) (Table 5).

**Table 5: Pivotal Study Third primary efficacy endpoint – Intention to Treat population**

	ADEPT	Control
Total number of patients	227	222
<b>Number of sites with dense adhesions</b>		
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)
<b>p-value for change</b>	<b>&lt;0.001 *</b>	<b>&lt;0.001 *</b>
Number of patients with fewer dense adhesions at second look	114 (50.2%)	109 (49.1%)
Odds ratio <sup>a</sup>		1.07
95.2% CI for odds ratio		0.72, 1.59
<b>p-value for treatment</b>		<b>0.73</b>
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).	
*	Statistically significant at the 0.1% level	

### Secondary efficacy (Per Protocol population)

In all (10) secondary efficacy variables, the use of ADEPT provided 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.

The following endpoints demonstrated statistical significance in favour of ADEPT:

- significantly greater reduction in the ADEPT group in the incidence of adhesions ( $p = 0.039$ ) with 76% of ADEPT-treated patients showing a reduction in adhesion incidence
- significantly more ADEPT patients were free of *de novo* adhesions at second look, 53% vs. 43%,  $p = 0.029$
- for the subgroup of patients presenting with a primary diagnosis of infertility, significantly more patients in the ADEPT group (52.9%) had a reduction in AFS score compared to control (30.4%),  $p = 0.001$ . In addition, there was a

significantly greater decrease in the AFS score in the ADEPT infertility patients than in the control,  $p=0.01$

- significantly greater reduction in the number of sites with visceral adhesions in the ADEPT group ( $p=0.046$ )

83% of ADEPT patients with pelvic pain as a primary diagnosis had a reduction in VAS pain score, mean reduction of  $35.8\pm 32.8$ mm,  $p<0.05$

#### Safety

The safety data indicated that ADEPT has a similar safety profile to control.

#### **DIRECTIONS FOR USE**

ADEPT is administered 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) *and removed all packs and sponges*, 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.

ADEPT should be warmed to approximately body temperature prior to use, using a device specifically intended for warming solutions in operating theatres. ADEPT may be kept in a warmer at 37°C for up to 14 days, provided it is not removed and then replaced. At all other times, storage below 4°C or above 30°C is not recommended.

Using standard operating room technique:

1. Remove the outer wrap from the ADEPT bag and hang the sterile bag of solution on a stand.
2. Remove the twist-off tab from the spike port and insert a standard giving set for connection to a laparoscope.
3. 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.
4. When used as an intra-operative irrigant solution, at least 100 mls of ADEPT should be introduced to the cavity every 30 minutes.
5. Remove remaining fluid before introducing the final instillation.
6. For the final instillation of ADEPT, prior to removal of the laparoscope, one liter (a new bag of ADEPT if 1 liter bags are being used) should be used. Direct the solution at the operative sites in the first instance, the remainder being distributed throughout the cavity.
7. Dispose of the bag and any unused portion of the solution following normal operating room biological hazard procedures.

The primary intended function of ADEPT is not to administer medicinal products. However, the bag has an injection port, which may be used for administration of drugs, if required. A range of antibiotics, including vancomycin, cephalosporins, ampicillin,

flucloxacillin, ceftazidime, gentamycin and amphotericin, have shown no evidence of incompatibility with ADEPT.

**HOW SUPPLIED**

ADEPT is packaged in single use, flexible polyvinylchloride bags, fitted with connecting ports, containing 1 liter or 1.5 liters of solution. The product is presented sterile (by heating in an autoclave). The bags are packaged in cartons of 10 x 1 liter or 5 x 1.5 liters.

**STORAGE**

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

**CAUTION**

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

**2. DRAFT SSED**

The draft is provided overleaf.

**ADEPT<sup>®</sup> (4% Icodextrin Solution)**

**SUMMARY OF SAFETY AND EFFECTIVENESS DATA**

**Draft Prepared by Innovata Plc; Not  
Yet Reviewed by FDA**

**ADEPT® (4% Icodextrin Solution)**

**SUMMARY OF SAFETY AND EFFECTIVENESS DATA**

**I. GENERAL INFORMATION**

*Device Generic Name:* Absorbable adhesion barrier (4% icodextrin solution)

*Device Trade Name:* ADEPT® Adhesion Reduction Solution

*Applicant's Name and Address:* Innovata plc (previously known as ML Laboratories plc)  
104a West Street  
Farnham  
Surrey  
GU9 7EN  
United Kingdom

*PMA Number:* P050011

*Date of Panel Recommendation:*

*Date of Notice of Approval to Applicant:*

**II. INDICATIONS FOR USE**

ADEPT Adhesion Reduction Solution is intended for use as an adjunct to good surgical technique for the reduction of post-surgical adhesions in patients undergoing gynecological laparoscopic surgery which may include adhesiolysis. ADEPT should be used as both an intra-operative irrigant and post-operative instillate during the surgery.

### III. DEVICE DESCRIPTION

ADEPT Adhesion Reduction Solution is a single use, sterile, clear, colourless to pale yellow fluid for intraperitoneal administration containing icodextrin (an  $\alpha$ -1,4-linked starch-derived glucose polymer) at a concentration of 4% w/v in an electrolyte solution.

Each 1 litre of solution contains:

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

Theoretical osmolarity 278 milliosmoles per litre

Ionic composition (approximately) per litre:

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 litre or 1.5 litres of solution. When stored at temperatures below 30°C ADEPT has a shelf life of 24 months. ADEPT should not be refrigerated or frozen.

### IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

#### Contraindications

ADEPT should not be used in patients with a known allergy to starch based polymers or in patients with maltose or isomaltose intolerance.

#### Warnings

ADEPT must be used as directed by a physician. It must not be used unless the solution is clear and the container undamaged.

Any unused portion of solution should be discarded. ADEPT is not to be used for intravenous infusion.

#### Precautions

The safety and effectiveness of ADEPT in children (patients less than 18 years of age) has not been evaluated.

The safety and effectiveness of ADEPT in pregnancy has not been evaluated. No clinical studies have been conducted in pregnant women although some women have

become pregnant within the first month after exposure to ADEPT. Therefore, this product is not recommended for use during pregnancy and avoidance of conception should be considered during the first complete menstrual cycle after use of ADEPT.

Foreign body reactions may occur with ADEPT, as with any implanted material.

The safety and effectiveness of ADEPT has not been evaluated in clinical studies in the presence of frank infections in the abdominopelvic cavity.

The safety of ADEPT has not been established after unintentional enterotomy or bowel perforation

Late onset (up to 14 days after instillation of device) severe abdominal-pelvic pain may present as a self limited symptom associated with normal temperature, normal WBC, present bowel sounds, and absence of peritoneal rigidity. This should be distinguished from peritoneal cavity infection, perforated bowel or other viscous, intraperitoneal bleeding, or other postoperative complications.

Pleural effusion may present as a self limited symptom which should resolve without intervention.

It is intended that 1 litre of ADEPT is instilled into the peritoneal cavity at the end of surgery. In clinical studies of ADEPT up to 2 litres of solution have been instilled (not adjusted for body weight). The safety of larger (than 2 litres) volumes and the efficacy of smaller (than 1 litre) volumes have not been established.

## V. ALTERNATIVE PRACTICES AND PROCEDURES

Practices intended to minimize adhesion formation 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 adjuvants such as crystalloid solutions. There are no commercially available devices approved for use in laparoscopic surgery as adjuncts intended to reduce post-surgical adhesions. Crystalloid solutions are used but generally in volumes considerably less than 1 liter.

## VI. 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 EU member states in October 1999. It has been marketed in the UK since June 2000 and is now marketed in the following 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  
 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 October 2005, from which a favourable risk-benefit profile has been generated thus far (see Section VII).

Since its launch onto the UK market a registry (ARIEL) was set up in Europe to enable a continuous evaluation of in-practice use of ADEPT. Leading European gynaecologists 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. A total of 4620 patients (2882 gynaecology and 1738 general surgery) were enrolled in the registry over a period of approximately 3 years between February 2000 and December 2003.

*ARIEL Gynecological Surgery Registry<sup>1</sup>*

This 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 (2.5% causally related) and 13.9% of laparotomy patients (3.9% causally related). The incidence of adverse events reflected rates expected in gynecological surgery.

*ARIEL General Surgery Registry<sup>2</sup>*

This 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 (3.7% causally related) and 30.6% of laparotomy patients (5.5% causally related). The reported frequencies of adverse events were in line with those published in the literature.

Icodextrin was originally developed by ML Laboratories plc (recently renamed as Innovata plc) as an alternative to glucose as the osmotic agent in peritoneal dialysis 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 and is regulated as a drug for use on a long term daily basis. It was initially approved for marketing in Europe in 1992 and subsequently licensed to Baxter Healthcare for use worldwide in renal failure. It has been marketed in Europe since 1994 and in the USA since 2003 under the tradename Extraneal™.

There is over 10 years experience with icodextrin in renal failure patients, reflecting at least 75,000 patient years of treatment experience, and more than 15,000 patients worldwide are currently receiving this treatment daily which has proven to be well-tolerated. This therefore provides a substantial safety database to support the clinical safety of ADEPT.

In 1999 ML Laboratories obtained drug registrations in Europe for 4% icodextrin solution as a vehicle for delivery of drugs into the peritoneal cavity. It is registered under the tradename Dexemel but is not actively marketed currently.

## **VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

### **1. Data from Clinical Studies**

ADEPT has been studied in three randomized, controlled US clinical trials involving a total of 548 patients undergoing gynecological laparoscopic surgery. Two safety studies enrolled a total of 99 (59 ADEPT treated, 40 control) patients and the third, a double-blind pivotal study, enrolled 449 (227 ADEPT treated, 222 control) patients.

No significant differences were observed in the incidence of adverse events, serious or non-serious, comparing 286 ADEPT treated and 262 control (Lactated Ringer's solution) patients over the period between the initial and second-look surgeries; ie up to 12 and 8 weeks in the pilot and pivotal studies, respectively.

In general, adverse events reported in the clinical studies were those typically expected following surgery and were generally mild to moderate and resolved either spontaneously or with routine post-operative care/medication.

In the double-blind pivotal study, the treatment groups were balanced with respect to the number of patients reporting adverse events overall, serious adverse events, and in terms of timing of events in relation to surgery. Overall, 221 (97.4%) ADEPT patients reported a total of 1065 events compared to 218 (98.2%) control patients who reported 1047 events (4.8 events per reporting patient per group).

In the pivotal study, the most common reported event was post-procedural pain followed by headache. Other prevalent events included nausea, post procedural discharge, dysmenorrhoea, constipation, and pelvic pain. Less common events included arthralgia, flatulence, urinary tract infection, abdominal pain, dysuria, nasopharyngitis, vaginal bleeding. (The vaginal bleeding events were not considered to be related to ADEPT or control and none was considered to be severe). Table 1

presents adverse events reported in  $\geq 5\%$  of patients (regardless of causality) in the pivotal trial.

**Table 1: 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 Population**

	ADEPT		Control	
	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
Post procedural discharge	31 (13.7%)	31	30 (13.5%)	30
Dysmenorrhoea	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
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) adverse events reported as treatment related were post procedural discharge (12.8% ADEPT; 10.4% control), post procedural pain (3.5% ADEPT; 3.1% control), abdominal distension (3.5% ADEPT; 1.8% control), and labia enlarged/vaginal swelling (3.5% ADEPT; 0.0% control). Apart from the post procedural pain which is an expected event following surgery, these events are probably the result of the presence of fluid in the peritoneal cavity. Labial edema is a recognised event associated with the use of fluids for irrigation and instillation in laparoscopic surgery<sup>3</sup> (see Section VII, 4 for further detail).

Other adverse events reported as related in the ADEPT-treated group included:  
*reported at an incidence of <2%:* abdominal pain, nausea, edema (including generalised and peripheral), and dysuria  
*reported at an incidence of <1%:* constipation, flatulence, application site swelling, chest pain, post operative fever, arthralgia, back pain, insomnia, bladder discomfort, pollakiuria, pelvic pain, pruritis generalised, and rash.

Analysis of the adverse event data from the three US controlled clinical studies combined does not change the risk benefit assessment for Adept. There are no events of clinical concern; most were mild to moderate, consistent with post-operative recovery, considered unrelated to study device by the investigator and resolved within a few days. The combined adverse event data from these three studies are consistent with all other safety data supporting the conclusion that Adept is safe when used as an abdominal instillate for adhesion reduction.

## 2. Post-marketing Experience

### 2.1 ADEPT

#### 2.1.1 Spontaneous Reports

From the marketing exposure of approximately 100,000 patients treated up to 1 January 2006 for use in any type of abdominal surgery, spontaneous serious adverse reactions, classified by the surgeon as causally related to treatment with ADEPT (i.e., definitely, probably, possibly, or not assessed) have been reported in 74 (37 gynecological, 27 general, and 10 unknown surgery) patients to 1 January 2006.

In gynecological laparoscopic surgery, 24 ADEPT – related spontaneous reports were received, involving 36 events. These are summarised by body system in Table 2.

**Table 2: Causally Related Serious Adverse Event Data From Spontaneous Reports Following Treatment With ADEPT In Gynecological Laparoscopic Surgery To 1 Jan 06**

Body System	Number of events*
Cardiac disorders	2
Gastrointestinal disorders	2
General disorders and administration site conditions	7
Immune system disorders	1
Infections and infestations	2
Injury, poisoning and procedural complaints	1
Investigations	1
Renal and urinary disorders	2
Reproductive system & breast disorders	13
Respiratory, thoracic and mediastinal disorders	4
Skin & subcutaneous tissue disorders	1
<b>TOTAL</b>	<b>36</b>

\* from 24 spontaneous reports (more than one body system may be involved in one spontaneous report)

All of the spontaneous reports are summarized and presented in detail by body system in Appendix 1 (in Table 1 (summary), and Tables 2A, 2B and 2C, for gynecological, general and unknown surgery types, respectively).

Seventeen of the cases were reports of labial swelling/vulval oedema (see Section VII, 4 for further detail) and the rest were of a mixed nature.

From this marketing exposure, there have been rare reports of hypersensitivity reactions in patients treated with ADEPT. (The incidence of patients experiencing hypersensitivity reactions is 0.02%).

### 2.1.2 *ARIEL Gynecological Surgery Registry*<sup>1</sup>

This included 2882 patients (2069 laparoscopies; 813 laparotomies).

In the laparoscopic cohort, the most common adverse events (% of procedures [% causally related]) were predicated irrigation / instillation events (1.88 [1.16]), haematological events (1.01 [0.05]) and pain (1.01 [0.43]). The most common adverse events associated with laparotomy procedures were septic/infective events (2.71 [0.00]), surgical / technical events (1.97 [0.37]) and pain (1.72 [1.35]). Postoperative ileus and vulval oedema were also reported, but at much lower incidence rates (0.14 [0.05] and 0.48 [0.34], respectively, in laparoscopic surgery; 0.98 [0.25] and 0.25 [0.25], respectively, in laparotomy surgery).

The incidence of adverse events by surgery type, safety panel preferred terms and causality (according to the surgeon classification of the event regarding relationship to treatment with ADEPT [i.e., definitely, probably, possibly related]) are presented in Table 3. The incidence of adverse events reflected rates expected in gynecological surgery

### 2.1.3 *ARIEL General Surgery Registry*<sup>2</sup>

This included 1738 patients (269 laparoscopies, 1469 laparotomies).

The most common adverse events (% of procedures [% causally related]) during laparoscopic surgery were septic/infective (3.35 [1.12]), surgical/technical (2.23 [0.00]), wound-healing problems (anastomotic; 2.23 [1.12]) and ileus (1.86 [0.00]). In the laparotomy cohort, the most common adverse events were septic/infective (4.15 [0.88]), respiratory (3.81 [0.20]), wound-healing problems (non-anastomotic; 3.81 [0.68]) and ileus (3.61 [1.09]). Overall 56 patients in the general surgery registry presented with symptoms of peritonitis, while only 4 post-operative incidences of peritonitis were reported as adverse events in both laparoscopy and laparotomy cohorts (incidences, 1.49 [0.74] and 0.27 [0.14], respectively). Patients presenting with peritonitis showed a slightly higher incidence of wound healing problems (5.4% vs. 3.4% for those without peritonitis). The incidence of anastomotic leakage among patients undergoing anastomotic procedures (n = 1049) was 3.1%; anastomotic leakage occurred in 7.6% (n=5) of 66 patients who underwent laparoscopy and 2.7% (n=27) of 983 patients who underwent laparotomy.

The incidence of adverse events by surgery type, safety panel preferred terms and causality (according to the surgeon classification of the event regarding relationship to treatment with ADEPT [i.e., definitely, probably, possibly related]) are presented in Table 4. The reported frequencies of adverse events were in line with those published in the literature.

**Table 3: ARIEL Gynecological Surgery Registry<sup>1</sup>**  
**AE Incidence As % Of Total Procedures**

SAFETY PANEL PREFERRED TERMS	GYNECOLOGICAL SURGERY							
	LAPAROSCOPY N=2069				OPEN SURGERY (INC. CONVERSIONS) N=813			
	ALL AEs		CAUSAL AEs		ALL AEs		CAUSAL AEs	
	N	%	N	%	N	%	N	%
<b>Allergy</b>	1	0.05%	1	0.05%	2	0.25%	2	0.25%
<b>Bowel perforation</b>	0	0.00%	0	0.00%	1	0.12%	0	0.00%
<b>Cardiac event</b>	1	0.05%	0	0.00%	2	0.25%	0	0.00%
Cardiac - Death	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Cardiac - No Death	1	0.05%	0	0.00%	2	0.25%	0	0.00%
<b>Fluid imbalance problems</b>	13	0.63%	9	0.43%	3	0.37%	2	0.25%
Other	3	0.14%	2	0.10%	1	0.12%	0	0.00%
Vulval oedema	10	0.48%	7	0.34%	2	0.25%	2	0.25%
<b>Haematological</b>	21	1.01%	1	0.05%	11	1.35%	0	0.00%
Haematological – Bleeding	16	0.77%	1	0.05%	7	0.86%	0	0.00%
Haematological – Other	4	0.19%	0	0.00%	0	0.00%	0	0.00%
Haematological - Pulmonary embolism	1	0.05%	0	0.00%	2	0.25%	0	0.00%
Haematological - Thrombosis	0	0.00%	0	0.00%	2	0.25%	0	0.00%
<b>Ileus</b>	3	0.14%	1	0.05%	8	0.98%	2	0.25%
Ileus – Mechanical	1	0.05%	0	0.00%	2	0.25%	0	0.00%
Ileus - Not Specified	1	0.05%	0	0.00%	2	0.25%	0	0.00%
Ileus – Paralytic	0	0.00%	0	0.00%	4	0.49%	2	0.25%
Ileus – Prolonged	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Ileus - Transient	1	0.05%	1	0.05%	0	0.00%	0	0.00%
<b>Pain</b>	21	1.01%	9	0.43%	14	1.72%	11	1.35%
Pain - Abdominal	7	0.34%	3	0.14%	2	0.25%	2	0.25%
Pain - Dysuria	1	0.05%	0	0.00%	0	0.00%	0	0.00%
Pain - Headache	1	0.05%	0	0.00%	0	0.00%	0	0.00%
Pain - Hypogastric region	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Pain - Lumbar	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Pain - Not specified	10	0.48%	5	0.24%	9	1.11%	8	0.98%
Pain - Psychogenic	0	0.00%	0	0.00%	1	0.12%	0	0.00%
Pain - Right hypochondrium	0	0.00%	0	0.00%	1	0.12%	0	0.00%
Pain - Upper Right quadrant	1	0.05%	0	0.00%	0	0.00%	0	0.00%
Pain - Shoulder	1	0.05%	1	0.05%	0	0.00%	0	0.00%
Pain - Suprapubic	0	0.00%	0	0.00%	1	0.12%	1	0.12%
<b>Predicated irrigation/instillation events</b>	39	1.88%	24	1.16%	13	1.60%	9	1.11%
Abdominal discomfort	3	0.14%	2	0.10%	2	0.25%	2	0.25%
Abdominal distension	8	0.39%	5	0.24%	1	0.12%	1	0.12%
Abdominal pelvic collections	7	0.34%	6	0.29%	2	0.25%	0	0.00%
Port/Wound leakage	21	1.01%	11	0.53%	8	0.98%	6	0.74%
<b>Respiratory (inc. Resp infections)</b>	0	0.00%	0	0.00%	3	0.37%	0	0.00%
<b>Septic/infective</b>	16	0.77%	2	0.10%	22	2.71%	0	0.00%
Septic/infective - Other	16	0.77%	2	0.10%	20	2.46%	0	0.00%
Septic/infective - Peritonitis	0	0.00%	0	0.00%	1	0.12%	0	0.00%
Septic/infective - Sepsis	0	0.00%	0	0.00%	1	0.12%	0	0.00%
<b>Surgical/technical</b>	19	0.92%	1	0.05%	16	1.97%	3	0.37%
<b>Wound healing problems - Anastomotic</b>	0	0.00%	0	0.00%	0	0.00%	0	0.00%
<b>Wound healing problems - Non Anastomotic</b>	3	0.14%	0	0.00%	10	1.23%	0	0.00%
<b>Other</b>	19	0.92%	4	0.19%	8	0.98%	3	0.37%
<b>TOTAL</b>	<b>156</b>	<b>7.54%</b>	<b>52</b>	<b>2.51%</b>	<b>113</b>	<b>13.90%</b>	<b>32</b>	<b>3.94%</b>

**Table 4: ARIEL General Surgery Registry<sup>2</sup>  
AE Incidence As % Of Total Procedures**

SAFETY PANEL PREFERRED TERMS	GENERAL SURGERY							
	LAPAROSCOPY N=269				OPEN SURGERY (INC. CONVERSIONS) N=1469			
	ALL AEs		CAUSAL AEs		ALL AEs		CAUSAL AEs	
	N	%	N	%	N	%	N	%
<b>Allergy</b>	0	0.00%	0	0.00%	3	0.20%	1	0.07%
<b>Bowel perforation</b>	2	0.74%	0	0.00%	3	0.20%	0	0.00%
<b>Cardiac event</b>	0	0.00%	0	0.00%	22	1.50%	1	0.07%
Cardiac - Death	0	0.00%	0	0.00%	12	0.82%	0	0.00%
Cardiac - No Death	0	0.00%	0	0.00%	10	0.68%	1	0.07%
<b>Fluid imbalance problems</b>	1	0.37%	0	0.00%	11	0.75%	4	0.27%
Other	1	0.37%	0	0.00%	10	0.68%	3	0.20%
Vulval oedema	0	0.00%	0	0.00%	1	0.07%	1	0.07%
<b>Haematological</b>	3	1.12%	1	0.37%	20	1.36%	0	0.00%
Haematological - Bleeding	2	0.74%	0	0.00%	13	0.88%	0	0.00%
Haematological - Other	1	0.37%	1	0.37%	3	0.20%	0	0.00%
Haematological - Pulmonary embolism	0	0.00%	0	0.00%	3	0.20%	0	0.00%
Haematological - Thrombosis	0	0.00%	0	0.00%	1	0.07%	0	0.00%
<b>Ileus</b>	5	1.86%	0	0.00%	53	3.61%	16	1.09%
Ileus - Mechanical	4	1.49%	0	0.00%	15	1.02%	5	0.34%
Ileus - Not Specified	1	0.37%	0	0.00%	18	1.23%	7	0.48%
Ileus - Paralytic	0	0.00%	0	0.00%	9	0.61%	2	0.14%
Ileus - Prolonged	0	0.00%	0	0.00%	11	0.75%	2	0.14%
Ileus - Transient	0	0.00%	0	0.00%	0	0.00%	0	0.00%
<b>Pain</b>	3	1.12%	1	0.37%	15	1.02%	4	0.27%
Pain - Abdominal	1	0.37%	0	0.00%	8	0.54%	2	0.14%
Pain - Dysuria	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Pain - Headache	1	0.37%	0	0.00%	0	0.00%	0	0.00%
Pain - Hypogastric region	0	0.00%	0	0.00%	1	0.07%	0	0.00%
Pain - Lumbar	0	0.00%	0	0.00%	1	0.07%	0	0.00%
Pain - Not specified	1	0.37%	1	0.37%	5	0.34%	0	0.00%
Pain - Psychogenic	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Pain - Right hypochondrium	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Pain - Upper Right quadrant	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Pain - Shoulder	0	0.00%	0	0.00%	0	0.00%	1	0.07%
Pain - Suprapubic	0	0.00%	0	0.00%	0	0.00%	1	0.07%
<b>Predicated irrigation/instillation events</b>	2	0.74%	1	0.37%	16	1.09%	12	0.82%
Abdominal discomfort	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Abdominal distension	1	0.37%	1	0.37%	6	0.41%	3	0.20%
Abdominal pelvic collections	0	0.00%	0	0.00%	6	0.41%	5	0.34%
Port/Wound leakage	1	0.37%	0	0.00%	4	0.27%	4	0.27%
<b>Respiratory (inc. Resp infections)</b>	3	1.12%	1	0.37%	56	3.81%	3	0.20%
<b>Septic/infective</b>	9	3.35%	3	1.12%	61	4.15%	13	0.88%
Septic/infective - Other	5	1.86%	1	0.37%	38	2.59%	9	0.61%
Septic/infective - Peritonitis	4	1.49%	2	0.74%	4	0.27%	2	0.14%
Septic/infective - Sepsis	0	0.00%	0	0.00%	19	1.29%	2	0.14%
<b>Surgical/technical</b>	6	2.23%	0	0.00%	43	2.93%	1	0.07%
Wound healing problems - Anastomotic	6	2.23%	3	1.12%	28	1.91%	9	0.61%
Wound healing problems - Non Anastomotic	2	0.74%	0	0.00%	56	3.81%	10	0.68%
<b>Other</b>	3	1.12%	0	0%	63	4.29%	6	0.41%
<b>TOTAL</b>	<b>45</b>	<b>16.73%</b>	<b>10</b>	<b>3.72%</b>	<b>450</b>	<b>30.63%</b>	<b>80</b>	<b>5.45%</b>

### 3. Data from Use in Other Indications

Most of the adverse effects from the use of 7.5% icodextrin (Extraneal) for peritoneal dialysis (PD) are related to the procedure of PD and are typical of those associated with the use of PD fluids. However, in patients with renal failure receiving daily icodextrin in conjunction with multiple other drugs, there have been common (<10%) reports of skin reactions, including pruritus and rashes which have been associated occasionally with exfoliation.

### 4. Potential Adverse Events

The vast experience with 7.5% icodextrin (Extraneal) together with clinical studies and marketing data from 4% icodextrin (ADEPT) has shown that icodextrin is well tolerated by patients.

There have been few adverse event reports attributed to the use of icodextrin solutions in its approved indications. Those that may be expected from use of ADEPT as an adjunct in gynecological surgery, in addition to those events that are generally expected from this type of surgery include the following:

It is possible that the patient may feel bloated for a short time, indicating the presence of fluid in the abdomen. Post procedural discharge is also possible.

Labial swelling/vulval edema has been reported both spontaneously from its marketed use and in controlled clinical studies. Thirty reports (17 spontaneous, serious, related, 13 solicited from ARIEL) have been received from marketing of ADEPT to 1 January 2006. Sixteen events were reported in the clinical studies (3 in the pilot studies and 13 in the pivotal study). All cases of labial edema were either self limited or treated symptomatically and they resolved without surgical intervention. Labial edema is a recognised event associated with the use of fluids for irrigation and instillation in laparoscopic surgery<sup>3</sup>. The edema results from fluid entering the labia from the peritoneal cavity via the Canal of Nuck or other fascial defects or planes. The fluid is typically resorbed spontaneously within a few days which is facilitated by bed rest and usually does not require drainage. However, if persistence of labial edema or evidence of secondary infection develops, then intervention may be necessary.

Other ADEPT-related adverse events from the pivotal study included:  
 reported at an incidence of <2%: abdominal pain, nausea, and dysuria  
 reported at an incidence of <1%: constipation, flatulence, application site swelling, chest pain, oedema (generalised, peripheral and face), post operative fever, arthralgia, back pain, insomnia, bladder discomfort, pollakiuria, pelvic pain, pruritis generalised, and rash.

There have been rare reports (0.02%) of hypersensitivity reactions in patients treated with ADEPT.

In patients with renal failure receiving daily icodextrin in conjunction with multiple other drugs, there have been common (<10%) reports of skin reactions, including pruritus and rashes which have been associated occasionally with exfoliation.

However, there have been only 3 ADEPT-related reports of skin reactions to date from marketing experience. In the pivotal study, in which patients may have been on other post-surgical medication, there were 19 reports of events in the skin and subcutaneous tissue disorders body system of which only 2 were considered to be ADEPT-related (cf 15 reports in Control group of which 1 considered related). Thus, including marketing exposure, the incidence of skin reactions in post surgical use with ADEPT is approximately 1 in 2,600 (0.04%) (regardless of causality), i.e. rare, or 1 in 13,000 (0.008%) (causally related), i.e. very rare.

Analysis of the AE data from the combined US clinical trials and the post marketing experience provides no evidence of an increased risk associated with the use of Adept in wider clinical usage.

## VIII. SUMMARY OF PRECLINICAL STUDIES

### Introduction

The preclinical data package which was used to support the approvals in Europe of 4% icodextrin solution as a medicinal product and a medical device was based on the data package generated to obtain marketing approvals firstly in Europe and then USA for the 7.5% icodextrin solution for peritoneal dialysis (PD). This package covers the studies which are generally required to obtain marketing approval for medicinal products and is discussed in section 1. The additional preclinical studies specifically conducted in support of 4% icodextrin solution as a medical device are discussed in section 2.

### 1. Preclinical Studies Conducted in Support of Peritoneal Dialysis (PD) Indication/General Requirements

#### 1.1 Introduction

In PD, the route of administration is by daily intraperitoneal (IP) infusion and drainage of 1.5 – 2.5 litres of icodextrin solution which 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, therefore, 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 both by ethical concerns and 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 maximise the IP dose and exposure of the animals, whilst 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.

The 'physiological' and 'pharmacological' consequences of PD had already been well studied in man. The toxicological investigations were focused on any local or systemic effects of icodextrin itself rather than of the procedure, so far as experiments could be done. The studies performed are therefore considered applicable to the proposed use of icodextrin for the reduction of post-surgical adhesions in which a 4% solution of icodextrin will be administered as a single dose on one occasion.

## ***1.2 Non-Clinical Pharmacology***

### ***1.2.1 General (Safety) Pharmacodynamics***

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

- conventional experiments (BP, cardiac activity respiration, response to IV noradrenaline) in the anaesthetised and instrumented New Zealand White Rabbit injected with up to 1mg/kg IV icodextrin;
- gastro-intestinal 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.

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

### ***1.3 Pharmacokinetics and Product Metabolism in Animals***

Icodextrin is a glucose polymer, isolated from starch, and composed of glucose residues joined largely through  $\alpha$ -1, 4 links with a small degree of branching through  $\alpha$ -1, 6 links. Thus its structure is similar to glycogen but with a lower degree of branching<sup>4</sup>.

Carbohydrates with structures like icodextrin are substrates for  $\alpha$ -amylase which is found in pancreatic juice, saliva and plasma. Alpha-amylase hydrolyses these carbohydrates to oligosaccharides, ultimately to maltose, isomaltose and maltotriose. These fragments are hydrolysed to glucose by maltase and isomaltase<sup>4</sup> found in the small intestine, kidney and a variety of other tissues<sup>5</sup>. Thus the end product of icodextrin metabolism is glucose, which will enter the body pool.

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 analysed for icodextrin and metabolites and the results are presented in Table 5 which includes data obtained from patients with and without renal function.

**Table 5: 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
Man (PD patients) <sup>6</sup>	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
Man with renal function	112.5g once daily IP for 32 days	Pre-dose (8)	0.002	0.010	2.12
		During treatment (39)	0.14	0.16	1.98
		Post treatment (9)	0.008	0.017	1.72

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

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.

#### 1.4 Toxicology

##### 1.4.1 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.

##### 1.4.2 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 hyperglycaemia 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.

#### 1.4.3 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 metabolised to mutagenic electrophilic groups.

#### 1.4.4 Reproduction 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.

#### 1.4.5 Local Toxicity Studies

##### 1.4.5.1 Irritancy

Specific studies have not been conducted but there is evidence from other studies that 20% icodextrin appears to be a reasonably bland 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.

#### 1.4.5.2 Peritoneal Macrophages and Polymorphs

The peritoneal cavity is normally sterile and it is assumed that sterility is maintained in part by the tidal activities of local and immigrating macrophages and polymorphs. Means to examine the numbers and activities of such cells have not been developed in a standardised way, but some screening experiments have been conducted using short-term cultures of human peripheral neutrophils (PMN) and peritoneal macrophages<sup>7</sup> 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 white cell functions, their relevance to *in vivo* host defences is unknown, and there was no clinical evidence of reduction in peritoneal defences.

#### *1.4.6 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 dextrin in local or distant tissues, including lymphoid organs and major viscera.
- Hyperplasia of the zona glomerulosa in the dog adrenals was seen which was probably 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. Preclinical Studies Conducted in Support of Adhesion Reduction**

### ***2.1 Preclinical Effectiveness Studies***

4% 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 four studies<sup>8</sup> has shown that 4% icodextrin solution used as a lavage during surgery and as an instillate (50ml) post-operatively significantly 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 whilst 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 demonstrated that both products significantly reduced adhesion formation in comparison to surgical controls, with no significant difference between the two products.

### *2.1.2 Rabbit Sidewall Model*

A further two studies<sup>8</sup> have 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<sup>8</sup>. 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 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 formal 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 lactated Ringer's solution 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. Therefore, ADEPT was shown to have no effect on the healing of bowel anastomoses and laparotomy incisions in the rabbit model.

### 2.2.3 Haemolysis

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

### 2.2.4 Effect on Peritoneal Metastasis

A rat adhesion model and rat tumor adhesion and growth model (using IP injection of the coloncarcinoma 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 (RPMI) and untreated (surgical) controls<sup>9</sup>. Perioperative intra-abdominal treatment with 7.5% icodextrin caused a 51% reduction in postoperative adhesion formation ( $p < 0.001$ ) of peritoneally traumatized rats 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. Therefore, icodextrin has been shown to be an effective solution in reducing postoperative adhesions without promoting tumor recurrence and thus may be used safely in oncological surgery.

## IX. SUMMARY OF CLINICAL STUDIES

### Introduction

ADEPT has been studied in the USA in two pilot studies and one double-blind pivotal study in female patients undergoing gynecological laparoscopic surgery with a planned second-look laparoscopy. The studies were conducted to evaluate the safety and efficacy of the device as an adjunct to good surgical technique in the reduction of post-surgical adhesions in comparison to Lactated Ringer's Solution (LRS). ADEPT or LRS was used as an intra-operative irrigant (100 mls every 30 minutes) in all studies. In the pilot studies 1 litre of ADEPT was instilled into the peritoneal cavity at the end of the surgical procedure in the first study, and up to 2 litres in the second study, whilst the volume of LRS was dependant upon the normal practice at the study centre. In the pivotal study, 1 litre of ADEPT or LRS was instilled at the end of the procedure. In all studies, the incidence, extent and severity of adhesions were assessed at 23 prospectively determined anatomical sites, using prospectively established scales for extent and severity, before laparoscopic adhesiolysis at baseline surgery and at second-look laparoscopy. Safety was evaluated based on adverse events recorded throughout the study, changes in clinical laboratory tests, post-operative recovery (changes in concomitant medication), and on gross adhesion evaluation at second-look.

## 1. Pilot Studies

The pilot studies were comparative, open-label, randomized, multicentre studies.

### 1.1 First Pilot Study

The first pilot study enrolled 62 patients (34 ADEPT-treated, 28 control) to evaluate the preliminary safety and use of the instillation of 1 liter of ADEPT compared to 'normal practice' volume instillation of LRS, in addition to the use of both solutions as an intra-operative irrigant (100 mls every 30 minutes). Female patients aged eighteen years and over were recruited for whom laparoscopic peritoneal cavity surgery was planned for pelvic pain and/or infertility problems which might require tubal and ovarian surgery. A total of 53 patients (27 ADEPT-treated, 26 control) met all protocol entry criteria and completed the second look laparoscopy at 6-12 weeks after first surgery. The incidence, extent and severity of adhesions were assessed at 23 pre-specified anatomical sites (Table 6) before adhesiolysis at baseline surgery and at second-look laparoscopy.

The change in overall number of adhesions between first and second laparoscopies for the per protocol population is presented below. In the ADEPT group there was a decrease in mean number of adhesions compared to baseline (5 down to 4.5). In the control group, the mean number of adhesions increased compared to baseline (2.9 up to 3.5). As baseline values are different, median values are also shown.

<b>INCIDENCE</b>	<b>First surgery</b> Mean (SD)	<b>Second-look surgery</b> Mean (SD)	<b>First surgery</b> Medians (min,max)	<b>Second-look surgery</b> Medians (min, max)
<b>ADEPT (n=27)</b>	4.96 (3.91)	4.48 (5.06)	5 (0,11)	4 (0,18)
<b>LRS (n=26)</b>	2.92 (2.92)	3.54 (3.28)	2 (0,9)	2 (0,12)

The safety profile was comparable for the 2 groups.

### 1.2 Second Pilot Study

The second pilot study enrolled 37 patients (25 ADEPT-treated, 12 control) to evaluate the preliminary safety and use of a larger instillation volume (up to 2 liters) of ADEPT compared to 'normal practice' volume instillation of LRS, in addition to the use of both solutions as an intra-operative irrigant (100 mls every 30 minutes). The same patient population as the first pilot trial was studied but the patients also had to have at least one adhesion present at baseline. A total of 30 patients (21 ADEPT-treated, 9 control) met all protocol entry criteria and completed the second look laparoscopy at 6-12 weeks after first surgery. The incidence, extent and severity of adhesions were assessed at 23 pre-specified anatomical sites (Table 6) before adhesiolysis at baseline surgery and at second-look laparoscopy.

The change in overall number of adhesions between first and second laparoscopies for the per protocol population is presented below. In both ADEPT and LRS groups there was a small decrease in mean number of adhesions compared to baseline with ADEPT giving a 10% and LRS a 9% improvement per patient. However, the study was primarily a safety study and due to the small number of patients involved was not

designed or powered to demonstrate a significant result in terms of efficacy.

INCIDENCE	First surgery	Second-look surgery	% improvement per patient
	Mean (SD)	Mean (SD)	Mean (SD)
ADEPT (n=21)	6.10 (2.49)	5.95 (3.96)	9.92 (46.03)
LRS (n=9)	8.22 (3.53)	7.56 (4.48)	8.94 (29.01)

The safety profile was comparable for the 2 groups indicating that a post-operative instillate of up to 2 litres ADEPT can be used without safety concerns.

## 2. Pivotal Study

The pivotal study was the largest and the only double blind, randomised clinical trial of an adhesion barrier device that has been conducted to date.

### 2.1 Study Design

The study was a comparative, double-blind, randomized, multicentre (up to 15 centers) study in approximately 450 gynecology patients to evaluate the efficacy and safety of ADEPT compared to LRS when both solutions were used as an intra-operative irrigant (100 mls every 30 minutes) and post-operative instillate (1 liter) in the reduction of post-surgical adhesions after gynecological laparoscopic surgery including adhesiolysis. Patients had at least three adhesions lysed using best surgical technique, while the pelvic-abdominal cavity was irrigated with (blinded) study solution; an instillate of one liter of study solution was left in the cavity on completion of surgery. Patients returned for a follow-up second look laparoscopy 4-8 weeks later.

The diagnosis and main criteria for inclusion in this study were:

- Female patients, aged 18 and over, in good general health including ASA (American Society of Anesthesiologists) score of two or less.
- Laparoscopic peritoneal cavity surgery was planned for a gynecologic procedure which included adhesiolysis.
- Patient agreed to a planned second-look laparoscopy for the study four-eight weeks after the initial surgical procedure.
- $\geq$  three of the available anatomical study sites contained adhesions.
- $\geq$  three of the anatomical sites with adhesions were lysed.
- None of the anatomical sites being scored for the purposes of this study were removed during the initial laparoscopy.
- All of the available anatomical sites (i.e. 23 sites if no previous removal of sites) could be visualized and recorded on the video tape during the course of the surgery.

### 2.2 Patient Assessment

#### 2.2.1 Efficacy:

The incidence, extent and severity of adhesions at 23 pre-specified anatomical sites (Table 6) were recorded on videotape and scored by the investigator at the baseline

(first) and second look surgeries. These adhesion scores were audited (by evaluation of the videotape recordings) by an independent, blinded reviewer.

### 2.2.2 Safety:

- Adverse events were recorded throughout the study;
- Laboratory values (hematology, biochemistry, urinalysis) were measured at baseline and follow-up visits and changes evaluated,
- Concomitant medications were recorded throughout the study and post-operative recovery was assessed by evaluation of changes in this medication,
- The incidence, extent and severity of adhesion data recorded for efficacy were grossly evaluated.

**Table 6: List Of 23 Anatomical Sites Evaluated In Pivotal And Pilot Studies.**

Anatomical Site
Caudal anterior peritoneum
Cephalad anterior peritoneum, right
Cephalad anterior peritoneum, left
Small bowel
Anterior uterus
Posterior uterus
Omentum
Large bowel, right
Large bowel, left
Large bowel, rectosigmoid portion
Cul-de-sac (posterior)
Right pelvic sidewall
Left pelvic sidewall
Lateral right ovary
Medial right ovary
Right ovarian fossa
Lateral left ovary
Medial left ovary
Left ovarian fossa
Right Fallopian tube
Right ampulla
Left Fallopian tube
Left ampulla

### 2.2.3 Patient accounting and demographic data

The study was conducted at 16 centers in the USA (only 15 active at any one time) over a three-year period (July 2001 – May 2004). 449 patients were randomized (227 ADEPT, 222 LRS) to the study and had the study solution instilled (Intention To Treat [ITT] population) and were assessed for safety. 402 patients (203 ADEPT, 199 LRS) completed the trial and were considered to be fully evaluable (Per Protocol [PP] population).

Table 7 presents the accounting, demographics, and baseline data for the pivotal study.

**Table 7: Pivotal Study Accounting, Demographics and Baseline Data**

	ADEPT	Control	Overall
No. patients randomized (Intention to Treat)	227	222	449
No. patients completed study (ie with second-look)	212	208	220
No. patients per protocol (Per Protocol)	203	199	402
Demographics:			
Age (yr) (mean±sd)	32.6±5.9	32.3±5.7	32.4±5.8
Height (in) (mean±sd) (n)	64.7±2.7 (225)	64.2±2.8 (221)	64.4±2.8 (446)
Weight (lb) (mean±sd) (n)	153.2±36.9 (225)	152.0±35.0 (220)	152.6±36.0 (445)
Race (n: %):			
Caucasian	160 (70.5)	144 (64.9)	304 (67.7)
East Asian	3 (1.3)	7 (3.2)	10 (2.2)
Afro-Caribbean*	32 (14.1)	32 (14.4)	64 (14.3)
Hispanic	24 (10.6)	35 (15.8)	59 (13.1)
Oriental	3 (1.3)	1 (0.5)	4 (0.9)
Other	5 (2.2)	3 (1.4)	8 (1.8)
No. of Sites with Adhesions at Baseline (mean±sd) (Intention to Treat)	10.27±4.26	10.34±4.39	10.31±4.32
Baseline AFS score for infertility subgroup (mean±sd) (Per Protocol)	8.98±9.86	8.20±9.88	8.57±9.86
Baseline mAFS score (mean±sd) (Per Protocol)	2.71±2.47	2.81±2.93	2.76±2.70
Operative Time (mins) (median) (Intention to Treat)	85.0	88.0	88.0
Days between first and second look surgery (Intention to Treat)	39.9±10.3	39.9±10.7	39.9±10.5

\* CRF term

## 2.4 Data analysis and results

### 2.4.1 Efficacy:

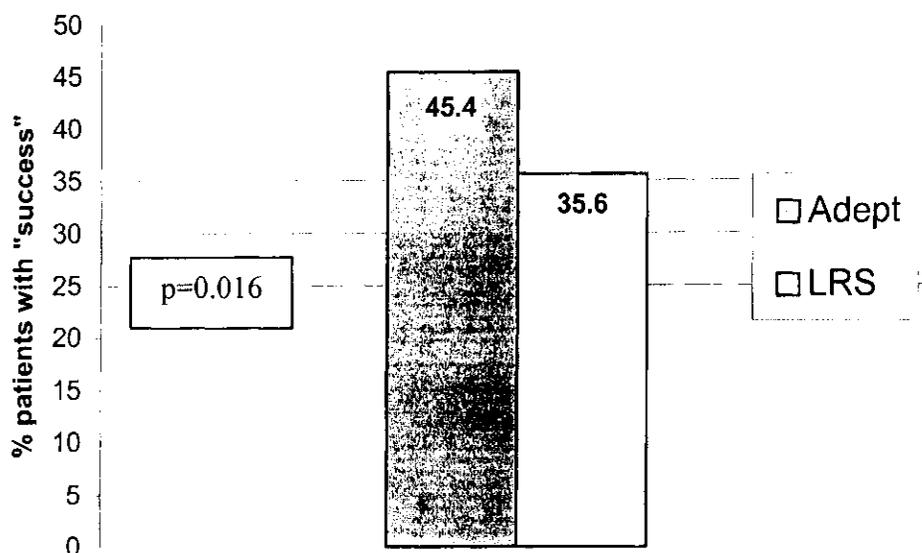
For efficacy, the primary variable was incidence of adhesions. Secondary variables included (incidence), extent, and severity of adhesions, American Fertility Society (AFS) score, modified American Fertility Society (mAFS) score, reformed and de novo adhesions, abdominal wall adhesions, visceral adhesions, and pain VAS score for patients with a primary diagnosis of pelvic pain.

The first primary efficacy endpoint was “success rate” which was defined as the proportion of patients for whom the number of sites with adhesions decreased by at least the larger of three sites or 30% of the number of sites lyzed.

Primary efficacy (Intention to Treat population)

1. A significantly greater percentage of patients, 45.4%, in the ADEPT group was defined as a “clinical success” compared to 35.6% in the control group (p=0.016, two-tailed test; p=0.008, one-tailed test) (Figure 1 and Table 8).

**Figure 1: Pivotal Study First primary efficacy endpoint (Percentage of patients achieving ‘success’) – Intention to Treat population**



**Table 8: Pivotal Study First primary efficacy endpoint – Intention to Treat Population**

	ADEPT	Control
Total number of patients	227	222
<b>Success<sup>a</sup></b>		
Number reporting	103 (45.4%)	79 (35.6%)
Difference in % of patients with success		9.8
sc		4.6
<b>95.2 CI for % of patients with success</b>		<b>0.7, 18.9</b>
Odds ratio <sup>b</sup>		1.64
95.2% CI for odds ratio		1.09, 2.46
p-value for treatment		0.016* (0.008)*

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 lyzed

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 (statistically significant at the 2.4% level, one-tailed)

2. 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 interval was less than zero in the ADEPT-treated patients (-2.83 to -1.62). In addition there was a significantly greater reduction in the number of sites with adhesions in the ADEPT treated patients compared with the control group ( $p = 0.047$ , two-tailed test;  $p = 0.023$ , one-tailed test) (Table 9).

**Table 9: Pivotal Study Second primary efficacy endpoint – Intention to Treat population**

	ADEPT	Control
Total number of patients	227	222
<b>Number of sites with adhesions</b>		
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
<b>LS mean for change<sup>a</sup> (95.2% CI)</b>	<b>-2.22 (-2.83, -1.62)</b>	<b>-1.60 (-2.24, -0.96)</b>
p-value for change	<0.001***	<0.001***
Difference between LS means <sup>b</sup>		-0.62
se		0.31
95.2% CI		-1.24, -0.004
<b>p-value for treatment</b>		<b>0.047* (0.023)*</b>

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 4.8% level, two-tailed (statistically significant at the 2.4% level, one-tailed)

\*\*\* Statistically significant at the 0.1% level

3. In the ADEPT group, 50% of patients had fewer sites with dense adhesions at second look ( $p < 0.001$ ); in the control group, the figure was similar (49%) (Table 10).

**Table 10: Pivotal Study Third primary efficacy endpoint – Intention to Treat population**

	ADEPT	Control
Total number of patients	227	222
<b>Number of sites with dense adhesions</b>		
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)
<b>p-value for change</b>	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>
Number of patients with fewer dense adhesions at second look	114 (50.2%)	109 (49.1%)
Odds ratio <sup>a</sup>		1.07
95.2% CI for odds ratio		0.72, 1.59
<b>p-value for treatment</b>		<b>0.73</b>

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).

\* Statistically significant at the 0.1% level

Secondary efficacy (Per Protocol population)

In all (10) secondary efficacy variables, the use of ADEPT provided 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.

The following endpoints demonstrated statistical significance in favour of ADEPT:

- significantly greater reduction in the ADEPT group in the incidence of adhesions (p=0.039) with 76% of ADEPT-treated patients showing a reduction in adhesion incidence
- significantly more ADEPT patients were free of *de novo* adhesions at second look, 53% vs. 43%, p=0.029
- for the subgroup of patients presenting with a primary diagnosis of infertility, significantly more patients in the ADEPT group (52.9%) had a reduction in AFS score compared to control (30.4%), p=0.001. In addition, there was a significantly greater decrease in the AFS score in the ADEPT infertility patients than in the control, p=0.01
- significantly greater reduction in the number of sites with visceral adhesions in the ADEPT group (p= 0.046)

83% of ADEPT patients with pelvic pain as a primary diagnosis had a reduction in VAS pain score, mean reduction of 35.8±32.8mm, p<0.05

The results for the secondary efficacy endpoints are summarized in Table 11.

Further analyses show that the benefit of Adept increases as the number of adhesion sites lyzed increases and that in patients with severe endometriosis Adept significantly reduces the adhesion burden. These investigations are summarized in Tables 12 and 13.

Table 11: Pivotal Study Secondary Efficacy Endpoints – Per Protocol population

VARIABLE / ENDPOINT	ADEPT	CONTROL	P-VALUE
<b>Incidence of sites with adhesions</b>			
Change from 1 <sup>st</sup> to 2 <sup>nd</sup> look (mean ± sd)	-2.64 ± 3.66	-2.02 ± 3.19	0.039*
% patients with reduction	76.4	69.3	0.121
Change from 1 <sup>st</sup> to 2 <sup>nd</sup> look excluding non-lyzed sites (mean ± sd)	-2.64 ± 3.66	-2.02 ± 3.19	0.068
% patients with four or fewer sites with adhesions at 2 <sup>nd</sup> look	32.0	28.1	0.510
Shift Analysis - % patients with 2 <sup>nd</sup> 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 <sup>d</sup>
<b>Severity of sites with adhesions</b>			
% change from 1 <sup>st</sup> to 2 <sup>nd</sup> look per patient (mean ± sd)	-24.2 ± 45.2	-21.5 ± 41.0	0.415
% patients with reduction	72.9	69.8	0.446
<b>Extent of sites with adhesions</b>			
% change from 1 <sup>st</sup> to 2 <sup>nd</sup> look per patient (mean ± sd)	-26.9 ± 51.4	-21.8 ± 48.5	0.240
% patients with reduction	77.3	69.8	0.084
<b>AFS score</b>			
Change from 1 <sup>st</sup> to 2 <sup>nd</sup> look for patients with a primary diagnosis of infertility (mean ± sd)	(n=102) -3.46 ± 6.77	(n=112) -1.10 ± 6.36	0.011*
% patients with a reduction (for patients with a primary diagnosis of infertility)	(n=102) 52.9	(n=112) 30.4	0.001**
Shift Analysis - % patients with 2 <sup>nd</sup> look scores grouped into 4 categories <sup>b</sup> (for patients with a primary diagnosis of infertility)	(n=102) minimal: 68.6 mild: 10.8 moderate: 11.8 severe: 8.8	(n=112) minimal: 59.8 mild: 13.4 moderate: 15.2 severe: 11.6	0.066 <sup>c</sup>
<b>Modified AFS score</b>			
Change from 1 <sup>st</sup> to 2 <sup>nd</sup> look	-0.67 ± 1.54	-0.48 ± 1.61	0.094
% patients with a reduction	70.4	69.8	0.722
<b>Reformed adhesions</b>			
Number of sites with (mean ± sd)	4.92 ± 3.91	5.11 ± 4.12	0.722
Number of sites without (mean ± sd)	3.77 ± 2.72	3.32 ± 2.29	0.065
% patients with at least one	87.7	86.9	0.832
<b>De novo adhesions</b>			
Number of sites with (mean ± sd)	1.13 ± 1.85	1.29 ± 1.61	0.036*
% patients with at least one	47.3	57.3	0.029*
<b>Abdominal wall adhesions</b>			
Change from 1 <sup>st</sup> to 2 <sup>nd</sup> look in no. sites (mean ± sd)	-1.17 ± 1.63	-0.94 ± 1.60	0.184
% patients with reduction from 1 <sup>st</sup> to 2 <sup>nd</sup> look in no. sites	65.5	58.3	0.129
<b>Visceral adhesions</b>			
Change from 1 <sup>st</sup> to 2 <sup>nd</sup> look in no. sites (mean ± sd)	-1.47 ± 2.62	-1.07 ± 2.22	0.046*
% patients with reduction from 1 <sup>st</sup> to 2 <sup>nd</sup> look in no. sites	68.5	63.3	0.228
<b>VAS score for pelvic pain</b>			
Change from screening to 2 <sup>nd</sup> look for patients with primary diagnosis of pelvic pain (mean [mm] ± sd)	(n=118) -35.8 ± 32.8	(n=108) -30.8 ± 30.2	0.995

\* statistically significant at the 5% level

\*\* statistically significant at the 1% level

<sup>a</sup> adjusted for 1<sup>st</sup> look incidence<sup>b</sup> four categories of AFS scores: minimal (score 0-5); mild (score 6-10); moderate (score 11-20); severe (score 21-32);<sup>c</sup> adjusted for 1<sup>st</sup> look AFS score

**Table 12: Increasing numbers of adhesions lyzed, definition of success: reduction of at least 3 sites or 30% of adhesions lyzed (PP)**

Adhesions lyzed	Adept		LRS		Difference in success rates (%)	95.2% confidence interval	p-value for treatment effect	Odds ratio
	Number of patients (n)	Success rate (%)	Number of patients (n)	Success rate (%)				
At least 3	203	49.3	199	38.2	11.1	1.3 – 20.8	0.018	1.67
At least 4	190	50.5	182	37.4	13.2	3.1 – 23.3	0.008	1.83
At least 5	168	53.6	161	38.5	15.1	4.3 – 25.8	0.004	2.02
At least 6	143	53.1	138	38.4	14.7	3.1 – 26.4	0.008	2.04

**Table 13: Number of sites with treated endometriosis at baseline**

Sites with treated endometriosis	Adept		LRS		Difference in success rates (%)	Odds ratio (95% CI)
	Number of patients (n)	Success rate (%)	Number of patients (n)	Success rate (%)		
0	89	56	87	40	16	2.31 (1.18, 4.49)
1-3	56	43	62	47	-4	0.84 (0.39, 1.83)
4-6	43	35	41	27	8	1.65 (0.63, 4.31)
>6	39	36	32	13	23	4.20 (1.19, 14.80)

#### 2.4.2 Safety:

Overall, there was little cause for safety concerns for the use of ADEPT or Control. Patients were exposed to a range of intra-operative washing volumes from 300-11000 ml, with 1000 ml of study device (ADEPT or Control) instilled at the end of surgery. This is a larger volume than has been used previously in clinical studies where solutions have been employed in an attempt to reduce post-surgical adhesion formation<sup>10</sup>.

Neither device was associated with an increase in the burden of adhesions; in particular patients receiving Adept had significantly fewer sites with adhesions at second look surgery than those in the LRS group  $p=0.039$  (PP population). There was an absolute decrease in the number of sites with adhesions in the Adept group ( $p<0.001$ ).

The treatment groups were balanced in terms of the adverse events experienced, with 1065 reports in the ADEPT group (4.8 per reporting patient), and 1047 in the Control group (4.8 per reporting patient). The majority (94.4%) of adverse events occurred in the time between the two laparoscopies.

Most of the reports were related in some way to the surgery, which all patients underwent, and were not considered related to study device (ADEPT 91.7%; Control 95.1% in the period between surgeries). In the small number of AEs that were

considered related to study device, there were slightly more in the ADEPT group, with the biggest differences between the groups seen in reports of abdominal distension, labial enlargement and dysuria. These events are probably the result of the longer residence time of fluid in the peritoneal cavity seen with ADEPT, associated with its assumed mechanism of prolonged hydroflotation. Labial enlargement was an expected side effect with vulval swelling noted in the patient information sheet.

Most AEs were "mild" or "moderate" (ADEPT 92.8%; Control 94.6%). For those few that were severe, the differences between the groups were in the number of reports of post-procedural pain, pelvic pain and headache. However, most of these reports were considered by the investigators not to be related to either device. Combining similarly termed pain AEs such as abdominal, pelvic, post-procedural, administration site and "post-operative analgesia" (reported as an AE) pain it was found that there were 211 ADEPT patients with 293 reports, and 214 Control patients with 288 reports, showing no excess of pain in the ADEPT group. There was also no excess of pain reported as serious in the ADEPT group.

There were some imbalances in AEs between the two groups. For ADEPT there were more reports of vaginal bleeding but none of these was considered by the investigators to be related to ADEPT, and none was considered severe, thus this was considered a fortuitous finding. For Control there were more reports of vomiting, diarrhea and post-procedural nausea.

There were no deaths during the study and 21 patients (8 ADEPT, 11 Control and 2 screen fail patients) reported 46 serious adverse events. Thirteen individual events from the 46 reported events were classified as possibly or probably related to the study device (seven ADEPT (all from one patient), six Control (from two patients)). All other events were considered unrelated or unlikely to be related to treatment. There was one withdrawal due to a serious adverse event (bowel perforation in a Control patient).

There were no clinically significant differences in changes in mean laboratory values or urinalysis between treatment groups, and no meaningful differences in the concomitant medication taken by either group.

## **2.5 Device Failures and Replacements**

During the US clinical studies there were two incidents that could be considered to be device failures and were reported to the FDA. Both incidents involved damage to packaging during transit and are summarized below:

*Report number PC0313, reported to the FDA 26 February 2001*

During the second pilot study (RAPIDS), fifteen bags of device were destroyed at trial site 2 at the request of ML Laboratories following notification by the site of damage to the boxes. The bags appeared to be intact. Replacement supplies were despatched. The bags had been supplied in immediate outer packaging boxes only. Outer shipping cartons were specified for future deliveries.

*Report number PC0519, reported to the FDA 30 April 2004*

During the pivotal study (PAMELA), six patient packs (703 to 708) were destroyed at trial site 2 under the instruction of ML Laboratories. The site had reported that the outer carton covering the pallet of boxes of supplies was ripped open, the inner boxes damaged and one bag was leaking. It was concluded that this had taken place during transit to or within the hospital. Supplies were replaced. This was the first such event. No further action was taken.

## **X. CONCLUSIONS DRAWN FROM THE STUDIES**

### **1. Safety**

A very substantial body of data is now available supporting the safety of ADEPT (4% icodextrin solution) in the peritoneal cavity.

ADEPT has been marketed in Europe for use in both laparoscopic and open gynecological and general surgery since 1999 and approximately 125,000 patients treated up to October 2005. During this time Adept has been the subject of extensive post marketing surveillance. The accumulated data supports the conclusion that ADEPT's use has not been associated with an increased incidence of adverse events.

Furthermore, icodextrin as a 7.5% solution (Extraneal) in the same electrolyte vehicle has been used for more than 10 years as a peritoneal dialysis fluid in Europe and was approved by FDA for this indication in December 2002. There are now at least 75,000 patient years of post marketing experience in this indication in which Extraneal is used on a daily basis in the long term.

The safety of ADEPT compared to Lactated Ringer's solution (LRS) has also been evaluated in three US controlled clinical trials, including the pivotal double-blind PAMELA study, in which it was used as an intraperitoneal instillate for adhesion reduction following gynecological laparoscopic surgery. In PAMELA, the overall incidence of adverse events in the two treatment groups was comparable and the pattern of reported events was generally similar between the groups. ADEPT treatment appeared to be associated with a slightly increased incidence of vaginal bleeding, abdominal distension, labial swelling and dysuria. These events are self-limiting; the vaginal bleeding was not considered treatment-related whereas the other events are believed to be due to the extended residence time of Adept in the peritoneal cavity.

The data from these controlled clinical trials demonstrate that ADEPT is safe when used as an abdominal instillate for adhesion reduction.

## 2. Effectiveness

The pivotal study, PAMELA, was a double-blind, randomized, multicenter study which compared the efficacy and safety of ADEPT with 1 liter LRS in the reduction of adhesions after laparoscopic gynecological surgery. PAMELA is the first study to compare an investigational device (ADEPT) with a control (LRS) in a double blind manner. Furthermore, it is the largest clinical study of an adhesion reduction agent undertaken to date, with a very rigorous determination of clinical success which was defined as a reduction in at least three adhesions. In contrast with other pivotal clinical studies, the control group here was not a 'gold-standard' regulatory-approved device, as LRS does not have a licence anywhere in the world for adhesion reduction. However, it is used during such surgical procedures in an attempt to reduce adhesion formation though usually in volumes of 200-500ml<sup>10</sup>. In general, LRS has not been shown to be effective in limiting adhesions when used in smaller volumes<sup>10</sup>.

PAMELA achieved its primary objective in demonstrating that, when used as an irrigant and as an instillate in patients undergoing gynecological surgery by laparoscopy, a significantly greater percentage of patients in the ADEPT group compared with the LRS group achieved "clinical success". This was a very rigorous determination of a clinical advantage, defined as the patients for whom the number of sites with adhesions decreased by the larger of three sites or 30% of the number of adhesion sites lyzed. 45.4% ADEPT patients were a 'clinical success' compared with 35.6% LRS patients (p=0.016 two-tailed; 0.008 one-tailed).

The level of success seen in the LRS group at 35.6% was much higher than expected, based on a wide range of published studies<sup>10,11</sup> and the open label pilot study, CLASSIC, on which PAMELA was based. CLASSIC suggested that a success rate of 25% could be achieved in the control group together with a difference of 15% between Adept and LRS, and with a sample size of 410 patients, the lower bound of the confidence interval (CI) could be 5% or above. However, the patient population in CLASSIC was not the same as in PAMELA e.g. not all CLASSIC patients had adhesiolysis; it was not a requirement of the CLASSIC protocol that patients should have at least three adhesions lyzed at first surgery, nor was it the case that every control patient had a whole liter of LRS instilled as a post-operative instillate. It is likely that this was the reason why the boundary of 5% for the lower confidence limit set for the first primary efficacy endpoint (which CLASSIC suggested might be achieved) was not achieved. (With the observed difference of approximately 10% the CI requirement would have needed an impractically large study involving 1500 patients. It is important to note that increasing the sample size modifies the limits of the CI but not the point estimate of the treatment difference.) These data nevertheless demonstrate the superiority of ADEPT over LRS as the percentage of women who achieved a clinically meaningful reduction of at least 3 adhesions with ADEPT is significantly greater.

The results for the second primary endpoint for the study clearly met the criteria defined in the protocol, i.e. ADEPT reduced adhesions. This result is in contrast to other studies in adhesion reduction where the test agent has increased the adhesion burden, but less so than in a control group<sup>11</sup>. The results of this study also show that there was a significantly greater reduction in the number of sites with adhesions with ADEPT than with LRS (p=0.047 two-tailed; 0.023 one-tailed). Taken together, the

first and second primary endpoints demonstrate that ADEPT provides a greater reduction in the adhesion burden than LRS.

There was no difference between ADEPT and LRS in the percentage of patients having fewer dense adhesions at second look, with about half of the patients in the study reporting a reduction in the number of sites with dense adhesions ( $p < 0.05$ ) for both ADEPT and LRS.

In PAMELA, for patients with a primary diagnosis of infertility, ADEPT patients had a statistically significantly greater reduction in AFS than LRS patients ( $p = 0.02$ ), and more of them had a reduction in AFS ( $p = 0.0016$ ).

For all the other secondary endpoints, there was a general trend in favor of Adept over LRS, with several of these differences reaching statistical significance.

Significantly more ADEPT patients were free of *de novo* adhesions at second look and had fewer visceral adhesions than LRS patients ( $p = 0.029$  and  $p = 0.046$  respectively).

ADEPT was effective in reducing adhesions. At baseline, patients ranged from a minimum of three to a maximum of 23 sites with adhesions, and ADEPT's advantage over LRS became more marked as the baseline number of sites with adhesions increased. Furthermore, ADEPT performed well in patients with endometriosis; again the difference between ADEPT and LRS became more marked with increasing number of sites with endometriosis.

Pelvic pain was significantly reduced in the ADEPT group ( $p < 0.05$ ), with a mean change of  $-35.8$  mm in VAS score, a reduction of 54%. Most (83%) ADEPT patients reported a reduction in pelvic pain.

### 3. Overall Conclusion

It is considered that the data from the pivotal study, in conjunction with safety data from approximately 125,000 patients treated for adhesions in Europe (in addition to at least 75,000 patient years experience in renal dialysis patients) unequivocally, demonstrate an acceptable risk/benefit profile for the device in adhesion reduction when used as an adjunct to good surgical technique. Furthermore, the study data demonstrate that ADEPT improves the surgical outcome of patients and has not been associated with an increased incidence of adverse events.

In summary, on the basis of the data available to date, ADEPT has been demonstrated to be an effective and well tolerated device to reduce post operative adhesions in patients undergoing gynecological laparoscopic surgery – a population for whom no adhesion barrier is currently available.

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**APPENDIX 1****CAUSALLY RELATED SERIOUS ADVERSE EVENT DATA  
FROM SPONTANEOUS REPORTS FOLLOWING TREATMENT  
WITH ADEPT TO 1 JAN 06**

- Table 1:** Summary of causally related serious adverse event data from spontaneous reports following treatment with ADEPT to 1 Jan 06
- Table 2A:** Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – Gynecological Surgery
- Table 2B:** Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – General Surgery
- Table 2C:** Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – Unknown Surgery



Table 2A: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – Gynecological Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
118	DE	F	36	1000ml	Postoperative tachyarrhythmias 5 hours post surgery	Serious unexpected	Possibly	Resolved	Diagnostic operative pelvic/laparoscopy with adhesiolysis and partial left salpingectomy and hysterectomy and fractioned abrasion. History: Apoplectic insult, questionable as paradoxical embolism over open oval foramen, interventional occlusion of an oval foramen, cholecystectomy. Con Meds: diclofenac, amoxicillin, midazolam, propofol, raprifun, procuromin, sevofluran, cefotiam. Minor residual shunt suspected after PFO occlusion.	Laparoscopy	Cardiac disorders
565	UK	F	35	Not known	Stroke	Serious unexpected	Not known	Not known	Adhesiolysis for dense adhesions in the right-vesical angle.	Not known	Cardiac disorders
128	UK	F	29	Not known	1. Signs of cardiac overload 2. Short of breath with respiratory crisis 3. Greater than expected bruising on abdomen	Serious unexpected	Possibly	Resolved	Laser procedure for endometriosis. Pt. drank 4l water within 24 hrs of surgery. Chest X-ray, blood pressure, blood normal. No shoulder tip pain. Symptoms resolved with frusemide within 24 hrs. Surgeon queried an allergic reaction.	Laparoscopy	Cardiac disorders, Respiratory, thoracic and mediastinal disorder, General Disorders and administration site conditions
162	DE	F	36	1000ml instillate	Peritonitis with Stapylococcus epidermidis, prevotella species	Serious unexpected	Probably	Resolved with sequelae	1. Abdominal hysterectomy with left adnectomy, removal of right ovarian section. 2. Adhesiolysis of a massive front-distended abdomen. Symptoms: Dysmenorrhaea, hypermenorrhea, adnexal tumour, endometriosis. History: Salpingectomy for inflamed bowel disease, rectum prolapse, laparotomy for adhesion ileus, adnexal tumour.	Not known	Gastrointestinal disorders

Table 2A: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – Gynecological Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
113	UK	F	29	1000ml irrigant, 1000ml instillate	1. Intraperitoneal haemorrhage 2. Abdominal swelling 3. Decreased blood pressure.	Serious unexpected	Probably	Resolved with sequelae	Division of adhesions and laparoscopy for pelvic pain.	Laparoscopy	Gastrointestinal disorders, Investigations
658	IT	F	47	Not known	Oedema of left lower abdominal quadrant also on the homolateral lower limb radix	Serious unexpected	Related	Resolved	Laparoscopic bilateral annexectomy for large ovarian cyst.	Laparoscopy	General Disorders and administration site conditions
261	UK	F	28	Not known	Anaphylaxis	Serious unexpected	Probably	Resolved	Type of surgery: Not known. History: Mild Asthma. Event details: Repeated anaphylactic reactions (3 on day 1, 2 on day 2, 2 on day 3) bronchospasm, angiodema, hypotension, moderate/severe hypoxia. No further information available.	Laparoscopy	Immune system disorders
653	UK	F	35	Not known	Peritonitis	Serious unexpected	Possibly	Resolved	Laparoscopic right salpingo-oophorectomy. No intra-operative complications. Post surgery patient presented with abdominal pain, distention and vomiting. Evidence of inflammation around the wound. Swab grew staph. Aureus and haemolytic group A Strep. Pt. underwent laparotomy which revealed peritonitis.	Laparoscopy	Infections and infestations

Table 2A: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – Gynecological Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
630	UK	F	40	1000ml instillate	Incisional hernia (in the left angle of the sheath)	Serious unexpected	Possibly	Resolved	Abdominal hysterectomy for an unknown cause.	Not known	Injury and procedural complications
169	UK	F	33	700ml	1. Fluid leaked from abdominal wound 2. Wound dehiscence day 8 post surgery	Serious unexpected	Possibly	Resolved	Right ovarian cystectomy and adhesiolysis History: Left salpingo-oophorectomy for endometriosis, right tube scarred	Laparotomy	Injury, poisoning and procedural complications
175	UK	F	82	Not known	Pfannenstiel wound dehiscence	Serious unexpected	Probably	Resolved	Pfannestiel left ovariectomy, total abdominal hysterectomy and right salpingo-oophorectomy for an ovarian mass History: Hypertension, atrial fibrillation, possibly pleural effusion.	Not known	Injury, poisoning and procedural complications
302	IT	F	Not known	Not known	Adhesions on uterine scar	Serious unexpected	Not known	Resolved	1 month post surgery thick adhesions on uterine scar - lysed via laparoscopy.	Laparotomy	Injury, poisoning and procedural complications
157	FR	F	Not known	Not known	Umbilical fistula (wall cavity) immediately after surgery.	Serious unexpected	Not known	Not known	Intra annexial hysterectomy. 10 days post surgery fistulous discharge was seen on the hysterectomy scar (Pondolfo)	Not known	Musculoskeletal and connective tissue disorders
2	UK	F	30	1000ml	Unable to urinate.	Serious unexpected	Probably	Resolved	Laparoscopic operation for ectopic pregnancy. Patient was unable to urinate 2 days after operation.	Laparoscopy	Renal and Urinary

Table 2A: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – Gynecological Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
293	FR	F	37	Not known	Day 1: post surgery oligo-anuria Day 2: renal insufficiency, creatineamia 331mmol/l Day 9: Effusion, febrile, CRP 381, false membrane covering the genital apparatus	Serious unexpected	Probably	Not known	Cystectomy (right) ovary under coeliosurgery. Creatineamia decreased after rehydration. Appendix appeared inflamed. Reporter considered causality of 'false membranes' only.	Laparoscopy	Renal and urinary disorders
127	UK	F	Not known	1000ml instillate	Vulval oedema	Serious expected	Related	Not known	Laparoscopic procedure for endometriosis.	Laparoscopy	Reproductive system and breast disorders
137	UK	F	Not known	Not known	Vulval oedema	Serious expected	Probably	Resolved	Resolved spontaneously.	Laparoscopy	Reproductive system and breast disorders
136	UK	F	Not known	Not known	Vulval oedema	Serious expected	Probably	Resolved	Resolved spontaneously.	Laparoscopy	Reproductive system and breast disorders
54	UK	F	32	1000ml instillate	Labial swelling	Serious expected	Almost certainly	Resolved	Initial surgery not known. No further information available.	Laparoscopy	Reproductive system and breast disorders
55	UK	F	38	1000ml instillate	Vulva swelling	Serious expected	Probably	Resolved	Adendometrioses ovarian cyst and adhesion.	Laparoscopy	Reproductive system and breast disorders

Table 2A: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – Gynecological Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
313	UK	F	18	300ml	1. Swelling of genitalia 2. Abdominal pain 3. Difficulty passing urine	Serious unexpected	Possibly	Resolved	Ovarian cystectomy.	Laparotomy	Reproductive system and breast disorders, Gastrointestinal disorders, Renal and urinary disorders.
52	UK	F	47	Not known	1. Vulval oedema 2. Abdominal oedema	Serious unexpected	Possibly	Resolved	Initial surgery not known. No further information available.	Laparoscopy	Reproductive system and breast disorders, General disorders and administrative site conditions.
119	UK	F	34	1000ml	1. Vulval oedema 2. Oedema of the anterior abdominal wall	Serious expected	Not known	Resolved	Laparoscopic laser for endometriosis and excision of right uterosacral ligament.	Laparoscopy	Reproductive system and breast disorders, General disorders and administrative site conditions.
111	UK	F	42	1000ml	1. Vulval oedema 2. Abdominal oedema 3. Rash on both forearms	Serious expected	Probably	Resolved	Ovarian cystectomy for asymptomatic endometriotic cyst. History: No known allergy. Asthma. Con meds: Morphine, antibiotics. Reported by patient.	Laparoscopy	Reproductive system and breast disorders, General disorders and administrative site conditions, Skin and subcutaneous tissue disorder

Table 2A: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – Gynecological Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
93	UK	F	33	Not known	1. Vulval oedema 2. Difficulty in breathing (bronchospasm)	Serious unexpected	Probably	Resolved	Laparoscopic endometriosis treatment. Treatment with steriods.	Laparoscopy	Reproductive system and breast disorders, Respiratory, thoracic and mediastinal disorders
140	UK	F	Not known	Not known	Pulmonary oedema	Serious unexpected	Possibly	Resolved	48 hours post discharge pt. presented with symptoms of respiratory distress & fluid on lungs. Antibiotics given.	Not known	Respiratory, Thoracic and mediastinal disorder
625	DE	F	30	1000ml	1. Pleural effusion 2. Minor pneumothorax 3. Minor pulmonary hypertension	Serious unexpected	Possibly	Resolved	Hysterosalpingocolposcopy with excision of an ovarian cyst. Con meds: cefuroxime 1.5g, calcium chloride dihydrate/magnesium chloride, 2 ampoules Panhenol and enoxaparin sodium (perioperative care). Med Hx: Pollenosis, and past extirpation of endometriosis focus left adnaxis, urinary bladder fold over and Douglas pararectal right.	Laparotomy	Respiratory, thoracic and mediastinal disorders
138	UK	F	39	1000ml instillate	1. Shortness of breath 2. Chest pain 3. Vulval and leg oedema 4. Itchiness night of surgery	Serious unexpected	Possibly	Resolved	Excision of left ovarian fibroma for fibroma and abdominal pain. ECG normal. Resolved with chlorphenamine. Reporter queried fluid overload. History: Pneumothorax.	Laparoscopy	Respiratory, thoracic and mediastinal disorders, General disorders and administration site conditions, Reproductive system and breast disorders

Table 2A: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – Gynecological Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
68	UK	F	Not known	Not known	Bleeding	Not Known	Not known	Not known	Initial surgery not known. No further information available.	Not known	Vascular disorders
67	UK	F	Not known	Not known	Bleeding	Not Known	Not known	Not known	Initial surgery not known. No further information available.	Not known	Vascular disorders
668	Germany	F	32	1000ml	Pneumonia Post operative peritonitis	Serious unexpected	Unrelated Possibly	Resolved	Hysterectomy for suspected recurrent endometriosis. Post operative diagnosis: complete obliteration of cavum Douglasi with elongation of sigmoid colon & suspected adenomyosis of uterus.	Laparoscopy	1. Respiratory, thoracic and mediastinal disorders 2. Infections and infestations 3. Gastrointestinal disorders
671	Greece	F	18	1000ml	Vulvar oedema & labial swelling	Serious expected	Possibly	Resolved	Ovarian cystectomy	Laparoscopy	1. Reproductive system and breast disorders 2. Reproductive system and breast disorders

Table 2A: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Feb 05 - 1 Jan 06 - Gynecological Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
674	UK	F	34	300ml	Burning sensation around right groin incision Large swelling around groin incision	Serious expected	Related	Ongoing	Adhesiolysis	Laparoscopy	1. Injury Poisoning and procedural complications 2. Reproductive system and breast disorders
687	UK	F	34	500ml	Orange size swelling over lateral port	Serious expected	Related	Resolved	Adhesiolysis. Clear fluid found collecting in subcutaneous tissue post surgery	Laparoscopy	General Disorders and Admin site conditions
688	UK	F	22	1000ml	Vulval oedema	Serious expected	Related	Resolved	Excision of endometriosis and adhesiolysis. Clear fluid in subcutaneous tissue	Laparoscopy	Reproductive system and breast disorders
692	Denmark	F	NK	NK	Hydrothorax	Serious unexpected	Not provided	Not provided	Unspecified length of time following surgery hydrothorax was experienced. Fluid was drained	Laparoscopy	Respiratory, thoracic and mediastinal disorders.

Table 2B: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – General Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
63	UK	M	39	Not known	1. Eosinophilia 2. Pyrexia	Serious unexpected	Possibly	Ongoing	Post surgery: Patient developed eosinophilia (3 days post surgery eosinophil count was 6.7 10 <sup>9</sup> /L) and was pyrexial (39°C) 3 hours after surgery but no infection was found, the patient was given antibiotics in case of postoperative chest infection in light of the raised white cell count. He was discharged 10 days post-op with elevated eosinophils. A physician stated 'suspected drug reaction, one of the medicines or ADEPT'. The reporter stated the events were 'possibly related' to ADEPT. Med Hx: ulcerative colitis, asthma, hay fever, allergy to mesalazine (causes vomiting). Previous surgery: colectomy and ileostomy (1990), reversal ileostomy and ileo-anal anastomosis (1991). Con meds salbutamol, salmeterol, beclamethasone inhalers.	Not known	Blood and lymphatic system disorders, General disorders and administration site conditions
74	UK	F	57	200ml	1. Bradycardia 2. Profound neurological sequelae 3. Cardiac arrest 4. Arrhythmia	Serious unexpected	Probably	Ongoing	Anterior resection of the rectum to remove small tumour, patient went into cardiac arrhythmia and cardiac arrest after approx 200 ml of ADEPT solution was instilled into the abdominal cavity.	Not known	Cardiac disorders

Table 2B: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – General Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
75	UK	M	64	1000ml	Myocardial infarction	Serious unexpected	Probably	Fatal	Proctocolectomy and ileostomy Med. History: MVR, previous MI, ulcerative colitis, carcinoma of rectum. Con meds: Warfarin, ACE inhibitors, frusemide, nizatide.	Laparotomy	Cardiac disorders, General disorders and administration site conditions
8	UK	M	41	1000ml	Dense fibrotic reaction found 10 days later at re-op, causing small bowel obstruction. Possible allergic response.	Serious unexpected	Possibly	Not known	Initial surgery not known. No further information available.	Not known	Gastrointestinal disorders
48	UK	F	43	1000ml instillate	Serosal bowel reaction	Serious unexpected	Not Known	Not known	Laparoscopic adhesiolysis.	Laparoscopy	Gastrointestinal disorders
115	UK	M	32	2000ml instillate	Peritonitis	Serious unexpected	Possibly	Resolved	Total colectomy for fulminant colitis (no perforation) and ileostomy. Med Hx: ulcerative colitis. Event led to acute resp. distress syndrome, renal failure	Not known	Gastrointestinal disorders
154	FR	F	26	Not known	1. Pelvic abscess 2. Occlusion 3. Very severe adhesions 4. Effusion	Serious unexpected	Not known	Discharged	Totalisation of colectomy with proctectomy and ileoanal anastomosis (reservoir surgery) to form a j-pouch for corticoid-resistant acute ulcerative haemorrhagic proctocolitis.	Not known	Gastrointestinal disorders

Table 2B: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – General Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
197	DE	F	68	1000ml	Diffuse purulent peritonitis	Serious unexpected	Possibly	Recovering	Anterior sigma-rectum resection. Exudate cultured; E. coli, Enterococcus faecialis Streptococcus and P. mirabilis found.	Not known	Gastrointestinal disorders
243	DE	F	19	1000ml instillate	1. Diffuse abdominal pain 2. Small intestinal perforation	Serious unexpected	Possibly	Resolved	Initial surgery: Adhesiolysis.	Laparotomy	Gastrointestinal disorders
338	UK	M	27	Not known	1. Intestinal obstruction 2. Severe adhesions	Serious unexpected	Not known	Not known	History: 2 previous surgeries.	Not known	Gastrointestinal disorders
640	EL	M	78	1000ml	Intestinal obstruction recurrence	Serious unexpected	Probably	Resolved with sequelae	Enteroplasty for acute intestinal obstruction. History: Chronic obstructive pneumonopathy and previous surgery for perforated duodenal ulcer. Obstruction found to be caused by adhesion.	Not known	Gastrointestinal disorders
661	IT	M	34	Not known	Intestinal adhesions (lack of efficacy)	Serious unexpected	Possibly	Not known	Patient underwent immediate laparotomy for adhesiolysis. Abdominal colic caused by a small bowel obstruction (volvulus in type) Pt. had 16 year history of adhesions with obstructions.	Laparotomy	Gastrointestinal disorders
651	FR	M	78	1000ml instillate	Sheathing plastic peritonitis	Serious unexpected.	Not known	Fatal	Patient underwent surgery for occlusion of small intestine. Patient underwent second surgery due to occlusions. Onset 78 days after surgery.	Not known	Gastrointestinal disorders

Table 2B: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – General Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
263	UK	F	38	1000ml instillate	1. Faecal peritonitis 2 Anastomotic leak 3. Intestinal fistula	Serious unexpected	Possibly	Resolved with sequelae	Laparoscopic ileocaecal resection for symptomatic long stricture in the terminal ileum. Hist: Crohn's disease, 3 previous laparoscopies.	Laparoscopy	Gastrointestinal disorders; Musculoskeletal and connective tissue disorders
300	IT	M	45	Not known	1. Intestinal occlusion 2. Viscero-parietal adhesions 3. Abnormality of mucose 4. Short bowel syndrome 5. Fistula	Serious unexpected	Not Known	Resolved with sequelae	Patient has long history of difficult bowel disease. Surgery: Adhesiolysis Med Hist: Laparocoele reduction by graft of polypropilene prosthesis (2001) Adhesiolysis (2002).	Not known	Gastrointestinal disorders; Musculoskeletal and connective tissue disorders
148	DE	F	38	Not known	Trocar hernia (x2)	Serious unexpected	Not known	Not known	Appendectomy for perforated appendicitis. Hernias occurred 2 months after use of icodextrin solution.	Not known	General disorder and administration site conditions
192	ES	F	63	Not known	1. Multi-organ failure 2. Toxic shock syndrome 3. Hypotension 4. Pyrexia	Serious unexpected	Possibly	Fatal	Vertical hemigastrectomy and internal bypass with duodenal anastomosis and cholecystectomy. Patient presented with morbid obesity.	Laparotomy	General disorders and administration site conditions; Infections and infestations, Vascular disorders

Table 2B: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – General Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
641	FR	F	77	Not known	1. Fever 2. Redness and itching of incision site 3. Urinary tract infection 4. Hypersensitivity	Serious unexpected	Not known	Discharged	Laparotomy for a right hemicolectomy with manual latero-lateral right ileo colic anastomosis, ganglionic clearing for adenocarcinoma and a cholecystectomy.	Laparotomy	General disorders and administration site disorders. Skin and subcutaneous tissue disorders
56	UK	F	36	Not known	1. Hypotension 2. Chest tightness 3. Decreased haemoglobin	Serious unexpected	Not known	Resolved	Appendectomy, adhesiolysis. Slow recovery. Hist. Asthma, ectopic pregnancy (3 months previously).	Laparoscopy	Vascular disorders, General disorders and administration site disorders, Investigations.
229	UK	F	66	Not known	Pulmonary oedema	Serious unexpected	Possibly	Resolved	Underwent surgery for acute appendicitis. Reporter stated it may be negative pressure pulmonary oedema although anaesthetist disagreed.	Not known	Respiratory, thoracic and mediastinal disorders

Table 2B: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – General Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
64	UK	F	37	1000ml	1. Adult respiratory distress syndrome 2. Infection	Serious unexpected	Possibly	Fatal	Indication: Laparoscopic surgery complicated by bowel perforation. Sigmoid colon puncture repair. ADEPT was instilled 20 hours later during laparoscopic surgery. Following surgery the patient experienced persistent fever, septicaemia, toxic shock, peritonitis, multi organ failure. Repeated negative blood and abdominal cultures although coliforms grown from various cultures, blood, wound and abdomen. No response to aggressive antibiotics IV. The reporter queried whether the patient experienced an allergic reaction to ADEPT causing adult respiratory distress syndrome. Med Hx: Previous general anaesthetic 4 days previously prior to another surgery. Con meds: Unknown.	Laparoscopy	Respiratory, thoracic and mediastinal disorder; Infections and infestations

Table 2B: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – General Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
648	FR	M	73	Not known	Contact eczema	Serious unexpected	Not known	Discharged	Right hemicolectomy with ganglionic cleaning and a manual latero-lateral right ileo-transverse anastomosis for an ulcerated infiltrating carcinoma, associated with a tubular adenoma. Med Hx: High blood cholesterol and arterial hypertension. Con meds: povidone-iodine (betadine) considered to be co-suspect. Reporter Causality: Probable for Povidone-iodine, not assessed for 4% icodextrin solution.	Laparotomy	Skin and subcutaneous tissue disorders
59	UK	F	27	Not known	Decreased haemoglobin	Serious unexpected	Possibly	Resolved	Subtotal colectomy for colitis, uneventful procedure. Med history: Colitis. Con Meds: Unknown.	Not known	Vascular disorders
669	Sweden	F	80	1500ml	Septic peritonitis	Serious unexpected	Possibly	Fatal	Hemicolectomy for colon carcinoma. Intra-abdominal proteus+++, E.coli ++, Bacteroides fragilis +.	Laparoscopy	Gastrointestinal disorders
675	Germany	M	61	1000ml	Pulmonary oedema Dyspnoea	Serious unexpected	Possibly	Resolved	Unspecified surgery for reduction of adhesions. Treated with furosemide, theophylline, methylprednisolone	Not known	Respiratory, thoracic and mediastinal disorders
676	Germany	M	57	1000ml	Pulmonary oedema	Serious unexpected	Possibly	Resolved	Surgery for adhesive strangulation of intestines. Therapy included forced diuresis	Not known	Respiratory, thoracic and mediastinal disorders

Table 2B: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – General Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
677	Germany	M	75	1000ml	Pulmonary oedema with spasticity	Serious unexpected	Possibly	Resolved	Surgery for reduction of adhesions. Treated with furosemide, theophylline, Solu-Decortin	Not known	1. Respiratory, thoracic and mediastinal disorders 2. Nervous system disorders

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Table 2C: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – Unknown Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
101	UK	Not known	Not known	Not known	Bladder leak	Not Known	Not known	Not known	Initial surgery not known. No further information available.	Not known	Event not coded, due to lack of information.
50	UK	Not known	Not known	Not known	Vomiting	Not Known	Not known	Not known	Initial surgery not known. Reporter noticed an increase in post operative nausea and vomiting in their patients. No further information available.	Not known	Gastrointestinal disorders
265	UK	F	Not known	Not known	1. Abdominal septic shock 2. Swelling of genitalia	Serious unexpected	Not known	Not known	Initial surgery not known. No further information available.	Not known	Infections and infestations, Reproductive system and breast disorders
100	UK	Not known	Not known	Not known	Anastomotic leak	Not Known	Not known	Not known	Initial surgery not known. No further information available.	Not known	Injury, poisoning and procedural complications
665	UK	F	42	Not known	Failure to absorb 4% icodextrin solution	Serious unexpected	Probably	Resolving	ADEPT still palpable as ascites 1 week later. Wound breakdown and 4% icodextrin solution oozed out.	Not known	Injury, poisoning and procedural complications
53	UK	F	Not known	Not known	Vulval oedema	Serious expected	Possibly	Resolved	Initial surgery not known. No further information available.	Laparoscopy	Reproductive system and breast disorders
62	UK	Not known	Not known	Not known	Vulval oedema	Not Known	Not known	Not known	Initial surgery not known. No further information available.	Not known	Reproductive system and breast disorders

Table 2C: Causally Related Serious Adverse Event Data from Spontaneous Reports Following Treatment with ADEPT to 1 Jan 06 – Unknown Surgery

Ref no.	Country	Sex	Age	Vol. used	Adverse event	Category	Causality Reporter	Outcome	Comment	Surgical Incision	Body system
679	France	F	34	Not known	Shock Rash (Urticaria) Hypotension	Serious unexpected	Not known	Resolved	Surgery unknown. Con Meds: Propofol, sufentanil citrate, Tracium, Perfalgan, Profenid, Cefacidal	Not known	1. Skin and subcutaneous tissue disorders 2. Vascular disorders. 3. Vascular disorders
690	Spain	F	NK	Not known	Haematocrit decreased	Serious unexpected	Not known	Not known	No other details provided other than patient did not have acute abdomen	Not known	Investigations
691	Not known	NK	NK	NK	Severe bleed	Serious unexpected	Not known	Fatal	No further details provided	Not known	Vascular Disorders

### **3. PRECLINICAL STUDY RESULTS**

#### **3.1 Summary of preclinical animal studies**

The summary is provided overleaf.

## SUMMARY OF PRE-CLINICAL ANIMAL STUDIES

### *PRE-CLINICAL STUDIES FOR PERITONEAL DIALYSIS INDICATION*

#### *Introduction*

Icodextrin 7.5% has been marketed in the UK since May 1994 for use in patients with chronic renal failure. It is licensed for use as a once daily replacement for a single glucose exchange of 6 to 12 hours duration in continuous ambulatory peritoneal dialysis (CAPD) and for the long daytime dwell (14 to 16 hours) in automated peritoneal dialysis (APD). The pre-clinical data package which was used to support the peritoneal dialysis (PD) marketing authorisation applications is discussed below.

In PD the route of administration is by regular intraperitoneal infusion and drainage of the icodextrin solution, which entails local exposure of the peritoneum and abdominal viscera, and systemic exposure, largely via passage into the lymphatics, and by transperitoneal absorption, to the polymer itself and its physiological breakdown products. The exposure is continuous.

Pharmacology and toxicity testing in animals was based, therefore, 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 both by ethical concerns and practical considerations about the feasibility of regular intraperitoneal instillation and drainage in experimental animals. The dosage administered was also sharply limited by the physiological consequences of instilling an increasingly hypertonic (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 maximise the IP dose and exposure of the animals, whilst 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.

The same considerations about acceptability and feasibility, plus concern over the validity of a test based on IP instillation of a hypertonic solution in pregnancy, led to the deliberate decision not to undertake Segment II or other reproduction toxicity tests for the PD indication.

The 'physiological' and 'pharmacological' consequences of intraperitoneal dialysis had already been well studied in man. The toxicological investigations were focused on any local or systemic effects of icodextrin itself rather than of the procedure, so far as experiments could be done. The studies performed are therefore considered applicable to the proposed use of icodextrin for the reduction of post-surgical adhesions in which a 4% solution of icodextrin will be administered on a single occasion.

### General (Safety) Pharmacodynamics

Conventional experiments in the anaesthetised and instrumented NZ White Rabbit (Report 239084) injected with icodextrin up to 1mg/kg IV did not show any major untoward effect on BP, cardiac activity or respiration, or on the response to noradrenaline IV. There was a small, transient increase in BP after each injection, not related to dose.

In the mouse, IP administration of icodextrin 100mg/kg IP had no effect on gastrointestinal transit time.

In organ bath studies, icodextrin up to 10% v/v had no particular action on spontaneous motor activity of isolated ileum and uterus, or on the responses of those tissues to autocooids.

Actions on the CNS were sought but were not found in the acute toxicity tests.

#### *Drug Interactions*

No specific study has been done, but there is no a priori reason to expect an effect of the polymer IP on the actions of conventional drugs.

#### *Conclusions*

Icodextrin acts as an osmotically active solute across the peritoneum. It appears to lack any other important or specific pharmacological activity in vivo or in vitro across a range of doses or concentrations and even after a local application to the peritoneum, which is directly exposed in man following IP administration.

These experimental observations have been amply confirmed in clinical practice in which Extraneal has been well tolerated over many years of intra-peritoneal application by patients in renal failure.

### Pharmacokinetics and Metabolism

Icodextrin is a glucose polymer, isolated from starch, and composed of glucose residues joined largely through  $\alpha$ -1, 4 links with a small degree of branching through  $\alpha$ , -1, 6 links. Thus its structure is similar to glycogen but with a lower degree of branching <sup>1)</sup>.

Carbohydrates with structures like icodextrin are substrates for  $\alpha$ -amylase which is found in pancreatic juice, saliva and plasma. Alpha-amylase hydrolyses these carbohydrates to oligosaccharides, ultimately to maltose, isomaltose and maltotriose. These fragments are hydrolysed to glucose by maltase and isomaltase <sup>1)</sup> found in the small intestine, kidney and a variety of other tissues <sup>2)</sup>. Thus the end product of icodextrin metabolism is glucose, which will enter the body pool.

To follow the metabolic rate of icodextrin through its metabolism to glucose and ultimately CO<sub>2</sub> it would have been necessary to obtain the polymer labelled with <sup>14</sup>C. This proved impractical and non-uniform labelling was rejected because the results

would not have been helpful. An assay was developed to separate and detect the icodextrin and its hydrolysis products in body fluids using gel permeation chromatography with on-line detection of eluting oligosaccharides. Concentration of oligosaccharides ranging from G1 (glucose) to G10 and high molecular weight structures (<G10) are expressed in mg/ml and is in % of the total carbohydrate in the sample.

Subsequent developments in HPLC techniques have permitted the use of ion chromatography as a more convenient procedure in determining the carbohydrates.

The fate of icodextrin administered in solution into the peritoneal cavity was determined by:

- (a) its stability in the peritoneal cavity
- (b) the degree of absorption into the systemic circulation and the amount recovered in the dialysate.
- (c) renal and metabolic elimination from the systemic circulation

Since the metabolic pathways for icodextrin like structures are known and animals with normal renal function would not have provided 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 intra peritoneal toxicity studies were analysed for icodextrin and metabolites as described above.

i) **Rat** - Icodextrin and its metabolites were not found in plasma samples taken on Day 1 and Day 28 of the study. Measurement of total carbohydrate in the urine showed considerable ( $\approx 30\%$ ) absorption from the peritoneal cavity with excretion as G1 to G10 and high molecular weight material (>G10). The results indicate absorption into the systemic circulation with rapid clearance by metabolism and renal excretion and low systemic exposure.

ii) **Dog** - Samples were analysed only from animals in the top dose group, owing to the complexity and time consuming nature of the assay and the failure to detect icodextrin and metabolites in rat plasma.

There was evidence of speedy absorption, as after treatment the total plasma carbohydrate level rose several-fold, comprising all the G1 to G10 oligomers and high MW material > G10. There was no evidence of cumulation during the 28-day treatment period.

In the urine, there was a prominent increase in the total content of carbohydrate and in the various oligomers. Overall, 12-74% of the instilled dose was excreted within 24 hours.

This demonstrates systemic exposure to icodextrin and its metabolic breakdown products, which was at least qualitatively similar to man, although the plasma levels were lower and overall clearance of the icodextrin was more rapid in the dog.

It should be noted that, in addition to renal excretion of polymer and metabolites the dog and rat have high plasma levels of maltase to convert maltose and maltotriose to glucose.<sup>2)</sup>

Rises in plasma glucose levels are noted in dogs in the pharmacokinetic and clinical chemistry (glucose oxidase) analyses.

The clearance of icodextrin in the rat and dog was faster than in CAPD patients, but there was sufficient general similarity between its handling in the three species, including systemic exposure, to indicate the validity of the animal experiments as models for man. Comparison of systemic exposure in test animals and man is usually used to assess the adequacy of pre-clinical studies. For icodextrin the mode of use, route of administration and kinetic differences between test animals with normal renal function and CAPD patients with extensive or complete renal failure make comparison of the usual parameters of limited value. However, a comparison of plasma levels during chronic dosing of test animals and CAPD patients has been made. In addition data from patients with renal function is also now available. See table overleaf.

The table below demonstrates the brief systemic exposure of the rat and the somewhat longer period in the dog, although both are less than in patients.

Species	Dose Details	Sample time (n)	Mean Plasma Levels (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	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
Man * with renal function	112.5g once daily for 32 days	Pre-dose (8)	0.002	0.010	2.12
		During treatment (39)	0.14	0.16	1.98
		Post treatment (9)	0.008	0.017	1.72

\* For patients with renal function plasma levels were calculated for G2, G3 - G7 and >G7 using ion chromatography with pulsed amperometric detection.

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. It will also be seen that the exposure to these substances of patients receiving IP treatment with 4% icodextrin is much the same as in patients being treated with Extraneal for CAPD. 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.

## TOXICOLOGY

### Single Dose Toxicity Tests

Limit dose experiments by the IP and IV routes have been done in the mouse and rat.

#### *Acute IV Toxicity Test (Limit dose) in the Mouse*

A 20% solution of icodextrin was administered by a single, slow (50 sec) IV injection to five male and five female young adult CD1 mice at a constant dose volume of 5 ml/kg. The maximum dose was 1000 mg/kg.

The mice were observed for 14 days following dosing. There were no deaths and no clinical signs were noted. At necropsy no abnormalities were detected.

The males showed possible slight retardation of weight gain but the females were unaffected.

#### *Acute IV Toxicity Test (Limit Dose) in the Rat*

A 20% solution of icodextrin was administered by a single, slow (50 sec) IV injection to five male and five female young adult Sprague-Dawley rats at a constant dose volume of 5 ml/kg. The maximum dose was 1000 mg/kg.

The rats were observed for 14 days following dosing. There were no deaths and no clinical signs were noted. At necropsy no abnormalities were detected.

#### *Acute IP Toxicity (Limit Dose) Test in the Mouse*

A 20% solution of icodextrin was administered by a single, slow intra-peritoneal injection to five male and five female young adult CD1 mice at a constant dose volume of 10 ml/kg. The maximum dose was 2000 mg/kg.

No effect was found on follow-up to autopsy after 14 days.

#### *Acute IP Toxicity Test (Limit Dose) Test in the Rat*

A 20% solution of icodextrin was administered by a single, slow intra-peritoneal injection to five male and five female young adult Sprague-Dawley rats at a constant dose volume of 10 ml/kg. The maximum dose was 2000 mg/kg.

No effect was found on follow-up to autopsy after 14 days.

### Conclusions

Single, high IV and IP doses of icodextrin had no acute systemic or local toxic effect in the mouse or the rat. No effect on the nervous system was observed despite the acute high dose treatment

The icodextrin was administered as a 20% solution in a balanced electrolyte solution, thus providing the maximum realistic concentration of icodextrin in the vehicle in which it will be supplied for clinical use. It might have been possible to administer a higher dose IP, but the solution would have been quite viscous, and, as shown in the subacute studies when this was done the only effects seen were caused by the osmotic load.

### Repeated Dose Toxicity Studies

The experiments done were designed to seek local and systemic actions as far as was permitted by the need to use IP administration.

In the rat, the only realistic experiment employed twice daily IP injections, but in the dog IP instillation and drainage by an implanted catheter was done, mimicking the treatment of PD patients. It was considered that surgical implantation of an abdominal catheter in the rat and treatment by repeated instillation and drainage would have been excessively stressful.

In both species the studies lasted for 28 days because it was not considered justifiable to expose the animals for longer to the stress and incidental risks of continuing the treatment, or to the repeated severe disturbance of fluid and electrolyte metabolism. The manner of use of peritoneal dialysis in man is designed to produce only very limited daily physiological changes.

As patients on CAPD, the main source of the safety database are virtually anuric, their treatment is adjusted to minimise the extent and acuity of the daily metabolic effects, whereas in the animals there is a repeated brief disturbance of fluid and electrolyte balance.

Patients using 4% icodextrin will have a relatively high degree of renal function, limited only by age, past disease and prior exposure to nephrotoxic therapies, so their status is closer to that of animals in the toxicity tests.

In addition, as icodextrin is more rapidly excreted by healthy animals than by anuric patients, the pattern of exposure in the toxicity tests differed sharply from that in patients.

The relatively short period of exposure in animals was a further strong reason for not attempting a longer repeat dose IP toxicity test in the rat, for example, in which it might have been feasible, but which was considered to be too remote a model of man to justify such a severe experiment.

In all the experiments the icodextrin was made up in the balanced electrolyte solution, used in clinical practice, and the latter was used as the vehicle control.

*Pilot 7-Day IP Toxicity Test in the Rat*

Although daily IP dosing is an accepted technique in toxicity testing, there was no experience of the repeated administration by this route of an osmotically active polymer solution, nor was the acceptable dose of icodextrin known.

Male Sprague-Dawley rats were dosed for 7 days at a dosage volume of 30ml/kg. Twice daily IP injections were given of icodextrin 14% and 20% (maximum concentration limited by the viscosity of the solution) and, as a comparator, the balanced electrolyte solution used as the vehicle.

The effects of treatment were to reduce food consumption and weight gain in both groups on icodextrin. On Day 8, the eosinophil count was reduced in the high dose group, BUN (markedly) and albumin (slightly) were reduced, and plasma chloride showed a small increase. Although the PCV and plasma Na were not changed, the pattern was attributed to the anticipated transient disturbance of fluid balance.

No important effect was seen at necropsy.

It appeared that the maximum tolerated dose (MTD) of icodextrin was 30ml/kg IP of a 20% solution, at least over 7 days.

*Pilot 28-day IP Toxicity Test in the Rat*

There was concern about the acceptability of daily IP injection of the large volume of icodextrin solution required to expose animals to the maximum tolerated dose of icodextrin, because use of more concentrated solutions was limited by their increasing viscosity. This pilot study in a small number of animals was done to explore the tolerability of icodextrin 30ml/kg of a 20% solution.

Ten male Sprague-Dawley rats were dosed twice daily by intra-peritoneal injection. Five rats were treated for 3 days and the other five for 28 days.

One rat died on day 11. This was considered due to the technical procedures of dosing and was unrelated to treatment with icodextrin.

On Days 2-4 there was variation in the daily weights of some rats attributed to the retention of fluid in the abdomen. 16.5ml peritoneal fluid was obtained from 1 rat by paracentesis 24h after the preceding dose, but in general fluid could only be collected in this way from a few animals in the first few days of treatment.

The other important findings, which did not differ between rats killed on Days 3 and 28, were of some bruising at the sites of injection, which was attributed to the trauma of the procedure, and a gelatinous appearance of the abdominal fat.

Inspection of the water bottles did not suggest a diuretic effect.

*28-Day IP Toxicity Test in the Rat with 14-Day Recovery Group*

One hundred and twenty-six Sprague Dawley rats were treated with either electrolyte solution, 5% glucose solution, 14% or 20% icodextrin. The glucose group was included because glucose solutions at concentrations of 1.36 - 4.25 % are used clinically for peritoneal dialysis. Each treatment was given as twice daily IP injections at a dose volume of 30 ml/kg for 28 days. Three males and three females from the electrolyte and icodextrin solution groups were retained for a 14 day off-test recovery period to investigate the reversibility of any effects observed. The total daily doses were icodextrin 8.4 and 12.0 g/kg/d, and glucose 3.0 g/d.

During the study period all the animals were observed at least twice daily for signs of ill health or reaction to treatment. Ophthalmoscopy was undertaken on all animals both pre-trial and on day 27. Haematology and clinical chemistry investigations were undertaken on days 8 and 28 and at the end of the recovery period. Urinalysis was undertaken over days 7/8 and 28/29. Peritoneal dialysate fluid was only recovered if the animals showed a distended abdomen. Histological evaluation was undertaken on 10 animals per sex from the electrolyte and 20% icodextrin groups.

There were 4 mortalities during the study (1 in the electrolyte group, 1 in the 14% icodextrin group and 2 in the 20% icodextrin group). These were attributed to the dosing procedure and not the test substance.

Distended abdomen was observed for the majority of treated animals, males in particular. This was considered to be attributable to retention of the instilled doses. On a few occasions small volumes of fluid were recovered from the abdominal cavity. The fluid tended to be slightly cloudy and pinkish in colour. Two of the 20% icodextrin treated animals had severe diarrhoea on day 3.

A lower body weight gain was recorded for males in the 14% icodextrin group and for both males and females in the 20% group. A reduction in food intake was observed for the icodextrin treated groups. No effect on water consumption was found, but there was the anticipated diuresis in the icodextrin - and glucose-treated groups and an increase in urine glucose.

The clinical chemistry tests indicated slightly lower BUN levels at day 7 for the icodextrin groups and a reduction in total protein and albumin for males from the 20% icodextrin group at day 28.

There were inflammatory changes noted around the injection sites at necropsy which were probably the local effect of multiple large injections. The special histochemical studies did not reveal any unusual storage of carbohydrate (PAS +ve) material in viscera or bone marrow from icodextrin - or glucose-treated animals. Electron microscopy of the spleen, mesenteric lymph nodes and liver showed some vacuoles in animals from all treatment groups, which may have been slightly increased in icodextrin-treated rats.

During the 14-day recovery period, there was effective normalisation of all the changes.

*Pilot 7-Day IV Toxicity Test in Beagles*

Icodextrin solution (in saline) was infused, intravenously, over a 4 hour period to two Beagle dogs (1 male, 1 female) at a dose volume of 10ml/kg/h. Over days 1-2 a 2.5% solution was infused. For days 3-4 a 10% solution was used and for days 5-7 a 20% solution was infused. The total dose was up to 88g/d per dog.

Blood samples were taken daily for haematological and biochemical testing. Blood and urinary levels of icodextrin were monitored. ECGs were taken daily prior to infusion and after 1h and at the end of infusion.

The procedure was well tolerated with no adverse clinical reactions and no effect on food intake and body weight. There was a slight reduction in plasma urea nitrogen levels for the female dog. Urinary sodium was increased and potassium and creatinine values were decreased over the 7 days. Creatinine clearance was slightly reduced on day 2, slightly increased on day 4 and reduced on day 7. Glucose was detected in the urine throughout the 7 days.

Histopathological studies showed some possible vacuolation of the liver in the male dog. These vacuoles did not contain fat or glycogen.

*Pilot 28-Day IP Toxicity Test in the Beagle*

This study was performed to investigate the feasibility of repeat daily administration and recovery of icodextrin via a peritoneal catheter. Peritoneal catheters were surgically implanted into six Beagle dogs. Following surgery the animals were administered electrolyte solution, 5% glucose solution or 14% or 20% icodextrin over periods of up to 28 days. Twice daily instillation of test fluids at 30ml/kg was employed, giving IP 'dwell' times of about 8 and 16 hours. Recovery of peritoneal fluid was undertaken prior to each administration.

The animals were observed on each day of the study with particular attention paid to any signs of abdominal distension. Blood, peritoneal fluid and urine samples were taken on most days. At the end of the study period each animal was subjected to a detailed post mortem examination with emphasis on the abdominal cavity and the appearance of the peritoneal surfaces.

The major clinical signs observed were abdominal distension and disturbances of food consumption. The abdominal distension was considered to be attributable to the retention of fluid. Some polydipsia and polyuria in dogs on icodextrin 14% or 20%, and glucose 5% was observed. BUN was lower in high-dose icodextrin - treated dogs.

Peritoneal fluid was quite often recovered from some of the dogs receiving icodextrin. Its protein concentration and white count varied in parallel but there were insufficient animals in the experiment to permit quantitative assessment of any dose-response relationship.

Autopsy showed only surgical scars and some fibrosis around the catheter.

The overall conclusion was that a procedure had been devised to permit a formal experiment, and that icodextrin 20% was the maximum achievable dose.

### Formal 28-Day IP Toxicity test in the Beagle with a 14-day Recovery Period

30 Beagle dogs were allocated to 4 treatment groups, receiving either electrolyte solution, 5% glucose, 14% or 20% icodextrin. The test materials were administered by peritoneal catheter at a dosage volume of 30ml/kg twice daily for 28 days. During the recovery period the animals were maintained on daily IP infusions of electrolyte solution.

All animals were observed daily for clinical signs with specific attention paid to signs of abdominal distension. The ECG of each animal was recorded pre-trial, on day 26 of treatment and after the recovery period. Ophthalmoscopy was performed pre-trial, on day 27 and after the recovery period. Blood and urine samples were collected from the icodextrin and electrolyte solution treated animals on days 1, 7, 14, 21 and 28 for haematology, clinical chemistry and urinalysis.

At the end of the study each animal was subjected to a detailed necropsy. In addition, special histochemical and electron microscope examinations were made of the liver, spleen and mesenteric lymph nodes to look for storage of icodextrin.

During the period of dosing there were occasional instances of abdominal distension due to retained fluid and food consumption was reduced in animals receiving glucose and icodextrin.

Peritoneal fluid was recovered only from animals receiving glucose and icodextrin. Its appearance and composition were broadly similar in all three groups, but the volume was greatly increased in animals on icodextrin. The recovered peritoneal fluid from glucose-treated dogs contained more protein and more leukocytes than that from animals receiving icodextrin 14 or 20%.

The dogs on icodextrin showed a dose-related increase in plasma glucose (up to 30%). Sodium levels tended to be slightly reduced and potassium levels were slightly higher for the 20% icodextrin treated group but the effects were too small to be of any biological importance. Urinary pH, volume and sodium were generally reduced. For the icodextrin treated groups specific gravity, potassium and creatinine were increased.

At autopsy there were no gross findings that were considered to be related to the test material. Some reddening of abdominal surfaces, thickening and adhesions were observed but these were attributed to the presence of the catheter or the procedure.

In the icodextrin treated animals there was decreased vacuolation of the adrenal zona glomerulosa and also hyperplasia. No other histological change was found in the other tissues and organs.

No storage vacuoles or retained carbohydrate were found in the special histopathological studies of the viscera.

In the recovery animals, the sole abnormality was incomplete return of the adrenal cortex to a normal appearance in dogs given icodextrin.

## Conclusion

As discussed above, ethical and practical considerations have limited the feasible toxicity experiments to 28 day studies. Further as described in previously, differences in the handling of icodextrin by the test species, affect evaluation of the tests. In the rat rapid excretion dominates the kinetics, and has resulted in limited systemic exposure despite daily instillation of up to 12g/kg/d. In the dog, however, the polymer persists for longer in the body, resulting in a degree of systemic exposure both to icodextrin and to its breakdown products. Although blood levels of icodextrin and its metabolic fragments were lower in the dog (about 10-25%) than are found in man, despite use of the much larger dose in the dog (up to about 12g/kg/d), there was extensive abdominal and systemic exposure of the animals to a mixture of carbohydrates qualitatively similar to that found in man.

It may be best to consider the experiments in the rat as an investigation focused more on the local effects in the abdomen of the repeated administration of Icodextrin, and on the urinary tract, and to regard those in the dog as a study of systemic and local actions under circumstances closer to man, albeit still influenced by the normal kidney function and metabolic differences in that species.

In both instances, it was considered that the maximum achievable dose had been administered.

In the rat, apart from the local effects of repeated IP needle punctures, the daily administration of up to 12g/kg Icodextrin had almost no effect on the animals, apart from some disturbance of food consumption and weight gain. There were small changes in plasma electrolytes and BUN, and in MCV, but the most that can be said is that they are consistent with the anticipated physiological effect of the treatment on fluid metabolism. What is more important is that the high local concentration of icodextrin had no effect on the peritoneum or abdominal viscera, nor was there any evidence of storage in the body.

The companion 28-day study in the dog was more stressful, as it involved IP surgical implantation of catheters and twice daily instillation and removal of a large volume of fluid from the peritoneal cavity. Despite that, the dogs withstood the procedure well.

The important findings were that icodextrin 20% (60ml/kg/d = 12g/kg/d) led to a sharp reduction in urine volume and the production of more concentrated urine, with no evidence of true renal failure, i.e. the treatment was acting as effective peritoneal dialysis, even in the presence of normal kidney function. This led to some reduction in plasma sodium, total protein and albumin levels, without a change in BUN or creatinine.

Plasma glucose showed a dose-related increase of up to 25-30% in animals on Icodextrin, which must be attributed to hydrolysis of the polymer as it is released from the peritoneal 'reservoir.' The dog also has high levels of circulating maltase to convert maltose and maltotriose to glucose.

A notable finding was hyperplasia and vacuolation of the zona glomerulosa in dogs in both groups receiving icodextrin. It is probable that this reflects increased secretion

of mineralocorticoids stimulated by the prolonged changes induced in fluid and electrolyte balance.

The effect on urine production and the induced change in sodium balance were better seen in the 7-day IV pilot test, albeit only in 2 dogs. It is likely that they were less apparent in longer term tests because of physiological compensatory changes and the less rapid effects on fluid balance produced by IP instillation.

Storage of the polymer was not found.

The overall pattern of changes in both species was of relatively slight effects on fluid and electrolyte balance, related to the duration of effective exposure to Icodextrin, of secondary adrenal cortical hyperplasia in the dog, and of mild hyperglycaemia in that species, too. 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.

No studies have been performed beyond 28 days

### **Reproduction Toxicity**

No experiments were done to support the renal dialysis indication.

There are several reasons why studies were not attempted. In part this was the impossibility even of paralleling the treatment of chronic renal failure in man with icodextrin, or of maintaining realistic exposure in animals, over the period required to investigate effect on reproduction.

Second, at least in a Segment II fetal toxicity and teratogenicity test, direct intraperitoneal instillation of icodextrin would put the enlarging uterus and adnexae at risk of much mechanical trauma and of any immediate consequence of the inescapable disturbance of the local milieu.

These are clear problems in animal experiments, which might not be paralleled in women, who have a relatively larger abdominal cavity.

Third, patients with end-stage renal failure are very rarely fertile, because of their physiological status. It is very unlikely that a pregnant woman either could or would be advised to continue to term, and if she did haemodialysis might become necessary, if only for mechanical reasons.

Last, the intensive toxicity tests did not show any histopathological signs of damage to gametogenesis or to the genital tract.

It was concluded, therefore, that in relation to the PD indication experimental data would be irrelevant in this very unusual instance, as any effect seen could be misleading, whether positive or negative.

Following discussions at the pre IDE stage, a single study in rats on the effects of icodextrin on fertility and embryo-fetal toxicity by IP administration was conducted.

It was concluded that icodextrin 20% 10ml/kg/day had no adverse effect on female condition, mating performance, fertility and embryo-fetal development. For males 20ml/kg/day had no effect on general condition, mating performance and fertility.

### **Mutagenicity**

#### *Ames Test*

No effect was found at up to icodextrin 10,000µg/plate.

#### *In Vitro Cytogenetic Test in CHO Cells*

In a very full test, icodextrin had no clastogenic effect in concentrations up to 200mg/ml, in the presence and absence of S9 microsomes.

This concentration did not affect the osmolality of the culture medium. It had no cytotoxic action.

#### *Mouse Micronucleus Test*

In a full conventional study, mice of both sexes were given icodextrin up to 6g/kg IP. In samples of bone marrow taken at several times no micronuclei were found.

#### **Conclusions**

Icodextrin does not possess chemical structures known to be or to be capable of being metabolised to mutagenic electrophilic groups.

It was negative in an Ames test and a cytogenetic test in vitro and in a mouse micronucleus test.

No further experiments have been done in vitro or in vivo because of the chemical nature of icodextrin, lack of activity even in very high concentrations in the in vitro studies, and because it is metabolised in vivo to compounds normally present in the body.

There is no realistic hypothesis to suggest that it might be mutagenic in vivo and so to justify further animal experimentation.

### **Carcinogenic Potential**

No experiment has been done.

As discussed above, no such test has been contemplated because of the bland chemical structure of icodextrin, and its breakdown products in vitro, its lack of genotoxic effect in vitro, and the impossibility of devising an appropriate and realistic animal experiment that would be physiologically acceptable.

## Local Toxicity Studies

### *Irritancy*

In view of the manner of use of icodextrin, information about local irritancy is particularly important.

A specific study of its effect on the peritoneum was not considered to be necessary because of the wealth of data available from other the acute and sub-acute tests.

Clinical and necropsy observations in the acute toxicity tests did not show any features of local irritation.

In the 7 and 28 day IP tests in the rat and dog, too, similar findings were made, reinforced by histological examination of the serosal and visceral peritoneum.

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, 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.

Thus, icodextrin 20% appears to be a reasonably bland solution for IP use, as, at the most, it may have caused only minimal irritation in animals, which is probably less than that due to the 5% glucose solution, which is in clinical use in PD.

### *Peritoneal Macrophages and Polymorphs*

The peritoneal cavity is normally sterile and presumably that state is maintained in part by the cidal activities of local and immigrating macrophages and polymorphs.

Means to examine the numbers and activities of such cells have not been developed in a standardised way, but some screening experiments have been done.

Using short-term cultures of human peripheral neutrophils (PMN) and peritoneal macrophages, icodextrin was found not to affect the viability of PMN, although it did diminish the uptake of zymosan and the subsequent respiratory burst. It was not itself an adequate medium to support the growth of *S. epidermidis*.

In independent experiments on THP-1 human monocyte cells, Icodextrin was found not to affect their viability or ability to kill phagocytosed *S. aureus* after retinoic acid-induced differentiation. Under certain experimental conditions it did reduce phagocytosis and chemotactic migration.

Both sets of experiments are based on very artificial conditions and it is not possible to relate them to in vivo circumstances. These results may also be compared with the repeated observation that the glucose solutions used for CAPD are capable of inhibiting chemotactic migration and even the phagocytic activity of polymorphs and macrophages in vitro.

It is important that in the 28-day toxicity tests, even in the dogs with an implanted peritoneal catheter, there was no evidence of intra-abdominal infection, and cells seen in peritoneal fluid and in the serosa did not appear abnormal.

It is a reasonable conclusion that repeated intraperitoneal instillation of icodextrin 20% does not appear to affect the defence functions of resident and migrant cells. That provides considerable reassurance that the IP use of 4% icodextrin is unlikely to pose a special threat to patients.

### Overall Conclusions

The pharmacodynamic tests show that icodextrin is inert under clinically relevant circumstances.

Sub-acute IP dosing in the rat had little effect, not even on fluid balance, possibly because of the rapidity of its excretion. In the dog, twice daily IP instillation for 28 days caused predictable reversible changes in fluid and electrolyte metabolism, and hyperplasia of the adrenal zona glomerulosa. The latter probably represents part of the counter-regulatory response to the physiological disturbances.

There was also a persistent moderate dose-related increase in plasma glucose in the dog, which was not produced by IP instillation of 5% glucose solution. The latter may well have been rapidly metabolised, as it did not produce as marked an effect on fluid balance.

Genotoxicity testing has been limited to two *in vitro* procedures (Ames and cytogenetics) and the *in vivo* micronucleus test. This is considered to be reasonable in view of the chemical nature of icodextrin and its metabolites and the circumstances of its use. Further experiments would neither be useful nor relevant.

Icodextrin did not cause local irritation of the peritoneum and adjacent structures. Although it may have had patchy effect in *in vitro* tests on certain white cell functions, their relevance to *in vivo* host defences is unknown, and there was no clinical evidence of failure of peritoneal defences.

The important points for clinical consideration, based on the non-clinical tests, are:

- i) 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 dextrin in local or distant tissues, including lymphoid organs and major viscera.

- ii) Hyperplasia of the zona glomerulosa in the dog was seen in the same experiment, in which it was probably part of a response to the disturbance of fluid and electrolyte balance produced in the toxicity test.

Both the effects in the dog were reversible.

iii) Drug interactions have not been studied, but there is no a priori reason to anticipate effects.

iv) The maximum duration of the toxicity tests is 28 days, no reproduction toxicity testing has been done, and the genetic toxicity testing has been limited to two in vitro and one in vivo procedures.

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## PHARMACODYNAMIC TESTS

### EFFECTS ON GI TRACT - CHARCOAL PROPULSION TEST

To assess the effect of icodextrin administered by the IP route on intestinal peristalsis.

Route	Species / Strain	No / Group	Dose	Charcoal Treatment	Observations
IP (RCC Report 239117)	Mouse NMRI		10ml/kg	0.3ml orally 60mins after test dose	The differences between the test and vehicle control groups were not shown to be statistically significant.  No significant reduction in charcoal propulsion in the atropine treated group. Probably due to 60 minute interval between dosing and charcoal administration.
		5 M	0.9% saline		
		5 M	0.25% icodextrin		
		5 M	0.5% icodextrin		
		5 M	1.0% icodextrin		
	5 M	20mg/kg atropine sulphate			

### EFFECTS ON THE RESPIRATORY AND CARDIOVASCULAR SYSTEMS

Route	Species / Strain	No	Dose	Treatment with Noradrenaline	Observations
IV (RCC Report 239084)	Rabbit New Zealand White	2 M	Successive applications of:  Control (0.9% saline) 2.5% icodextrin 5% icodextrin 10% icodextrin  1ml/kg at 20min intervals	2.5µg/kg 10 mins after test dose	<i>Blood pressure:</i> Slight and transient increase immediately following icodextrin dose <i>Heart rate:</i> Slight and transient decrease immediately following icodextrin dose <i>Respiration rate:</i> No effect <i>Noradrenaline:</i> No significant modification of effect

## PHARMACODYNAMIC TESTS (cont.)

### EFFECTS ON SMOOTH MUSCLES (IN VITRO)

<i>Principle:</i>	To assess the effects of ascending concentrations of icodextrin on agonist induced contractions of isolated guinea pig ileum.
<i>Species / strain:</i>	Ibm: GOHI albino guinea pig
<i>Ileum preparation:</i>	Longitudinal strips fixed in organ bath and pre-stretched (tension approx. 1 gram)
<i>Test substance:</i>	2.5%, 5%, 10% and 25% icodextrin in Tyrode soln.
<i>Standard agonists:</i>	Histamine 0.0001 µg/ml, 0.001 µg/ml, 0.01 µg/ml, 0.1 µg/ml and 1 µg/ml Acetylcholine 0.0001 µg/ml, 0.001 µg/ml, 0.01 µg/ml, 0.1 µg/ml and 1 µg/ml Barium chloride 1 µg/ml, 3 µg/ml, 10 µg/ml and 30 µg/ml
<i>Standard antagonists:</i>	Diphenhydramine 0.1 µg/ml Atropine 0.01 µg/ml Papaverine 2.5 µg/ml
<i>Results:</i>	No agonist activity was observed. At 2.5, 5 of 10% v/v icodextrin did not significantly affect histamine, acetylcholine or barium-induced contractions. At 25%v/v icodextrin shifted the concentration-response curve slightly to the right. This finding was not considered to be pharmacologically significant. The high concentrations of test substance per organ bath content are likely to affect the tissue because of its high viscosity.

<i>Principle:</i>	To assess the effects of ascending concentrations of icodextrin on agonist induced contractions of isolated rat uterus.
<i>Species / strain:</i>	BRL Han Wistar rat
<i>Uterus preparation:</i>	Each horn was fixed in the organ bath and pre-stretched (tension approx. 1 gram)
<i>Test substance:</i>	2.5%, 5%, 10% and 25% icodextrin
<i>Standard agonists:</i>	Oxytocin 0.001 µg/ml, 0.01 µg/ml, 0.1 µg/ml, 1 µg/ml and 10 µg/ml
<i>Results:</i>	2.5% icodextrin did not affect oxytocin induced contraction of the uterus preparation. 5 and 10% icodextrin shifted the concentration/response curve slightly to the right. At 25% icodextrin the concentration/response curve was shifted to the right. This finding was not considered to be of pharmacological significance because of the high test article concentrations in the organ bath.

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**SYSTEMIC TOXICITY  
SINGLE DOSE STUDIES**  
with 14 day follow-up period

Route	Species / Strain	No.	Dose	Observations
IV (IRI Report 6464)	Mouse CD1	5 M, 5 F	20% icodextrin at 5ml/kg (max dose 1000mg/kg)	<i>Clinical signs</i> - No adverse reactions or deaths <i>Body weight</i> - Slight retardation of weight gain in males <i>Necropsy</i> - No abnormalities detected
IV (IRI Report 6463)	Rat Sprague-Dawley	5 M, 5 F	20% icodextrin at 5ml/kg (max dose 1000mg/kg)	<i>Clinical signs</i> - No adverse reactions or deaths <i>Body weight</i> - Unaffected by treatment <i>Necropsy</i> - No abnormalities detected
IP (IRI Report 6466)	Mouse CD1	5 M, 5 F	20% icodextrin at 10ml/kg (max dose 2000mg/kg)	<i>Clinical signs</i> - No adverse reactions or deaths <i>Body weight</i> - Slight retardation of weight gain <i>Necropsy</i> - No abnormalities detected
IP (IRI Report 6465)	Rat Sprague-Dawley	5 M, 5 F	20% icodextrin at 10ml/kg (max dose 2000mg/kg)	<i>Clinical signs</i> - No adverse reactions or deaths <i>Body weight</i> - Unaffected by treatment <i>Necropsy</i> - No abnormalities detected

**MULTIPLE DOSE STUDIES IN THE SPRAGUE-DAWLEY RAT**

Route	Duration	No. / Group ( )	Dose 30 ml / kg twice daily	Observations
IP (IRI Report 7390)	7 days	(1) 5 M (2) 5 M (3) 5 M	Electrolyte soln 14% icodextrin soln 20% icodextrin soln	<p><i>Clinical signs</i> - No adverse reactions or deaths</p> <p><i>Body weight</i> - Reduced in groups 2 and 3</p> <p><i>Food consumption</i> - Reduced in groups 2 and 3</p> <p><i>Water Consumption</i> - No treatment related differences between groups</p> <p><i>Haematology</i> - Marked reduction in eosinophils for group 3</p> <p><i>Biochemistry</i> - ↓ BUN, ↓ albumin ; ↑ chloride for groups 2 and 3</p> <p><i>Necropsy</i> - No treatment related findings</p>
IP (IRI Report 7400)	3 days 28 days	(1) 5 M (2) 5 M	20% icodextrin soln	<p><i>Clinical signs</i> - 1 death due to technical procedure of dose administration (group 2). Distended abdomen in group 2</p> <p><i>Body weight</i> - Unaffected by treatment</p> <p><i>Necropsy</i> - Abdominal bruising probably related to dosing procedure. Gelatinous appearance of fat within abdominal cavity for group 2</p>
IP (IRI report 7423)	28 days	(1) 19 M, 19 F (2) 6 M, 6 F (3) 19 M, 19 F (4) 19 M, 19 F  Groups 1, 3 and 4 included 3 M and 3 F rats retained for a 14-day recovered period. Groups 1, 3 and 4 also included 4 M and 4 F rats used in blood level and excretion studies.	Electrolyte soln 5% glucose soln 14% icodextrin soln 20% icodextrin soln	<p><i>Clinical signs</i> - 4 deaths attributed to procedure (groups 1, 3 and 4). Scabbing on shoulders and slight hair loss in majority of animals attributed to administration procedure. Distended abdomen for majority of animals Severe diarrhoea in 2 males in group 4.</p> <p><i>Body weight</i> - ↓ body weight gain in icodextrin groups.</p> <p><i>Food and water consumption</i> - ↓ food intake in icodextrin groups.</p> <p><i>Ophthalmoscopy</i> - No treatment related changes.</p> <p><i>Haematology</i> - No changes attributable to treatment</p> <p><i>Biochemistry</i> - BUN levels lower in icodextrin groups at day 7. Total protein and albumin ↓ for males in group 4 on day 28.</p> <p><i>Urinalysis</i> - Sodium &amp; potassium ↓ in group 3 and 4. Potassium ↑ in group 2. Volumes and SG ↑ in group 2, 3 and 4.</p> <p><i>Necropsy</i> - Inflammatory changes around injection sites probably related to dosing procedure. No histological changes related to treatment. Increased incidence of vacuolation in cytoplasm of hepatocytes in males in groups 3 and 4.</p> <p><i>Recovery animals</i> - Effective normalisation of all changes during 14-day recovery period.</p>

### MULTIPLE DOSE STUDIES IN THE BEAGLE DOG

Route	Duration	No	Dose	Observations
IV (IRI report 5062)	7days	1 M, 1 F	<p>4 h period daily 10ml/kg/h</p> <p>2.5% Days 1 - 2 10.0% Days 3 - 4 20.0% Days 5 - 7</p> <p>Total daily dose approx. 1, 4 or 8 g / kg</p>	<p><i>Clinical signs</i> - No adverse clinical reactions</p> <p><i>Body weight</i> - Unaffected by treatment</p> <p><i>Food consumption</i> - Unaffected by treatment</p> <p><i>Haematology</i> - Some transient changes. However no adverse effects attributed to treatment.</p> <p><i>Biochemistry</i> - Slight reduction in plasma urea nitrogen for female dog. Slight ↑ in creatinine on day 7.</p> <p><i>Urinalysis</i> - SG ↑ on days 5-7. Sodium ↑, potassium and creatinine ↓. Creatinine clearance ↓ on day 2, ↑ on day 4 and ↓ day 7. Glucose in urine over 7 day dosing period.</p> <p><i>Histopathology</i> - male dog ↑ vacuolation of cytoplasm of hepatocytes not associated with cell injury.</p>
IP (IRI Report 7672)	8-29 days	4 M, 2 F	<p>30 ml/kg twice daily</p> <p>1M 20% icodextrin days 1,2,6,7,8 2F 20% icodextrin days 1-9 electrolyte soln days 10-15 5% glucose days 16-21 20% icodextrin days 22-28 5% glucose days 28-29</p> <p>3M 14% icodextrin days 1-11 days 14-18</p> <p>4M 20% icodextrin days 1-29</p> <p>5M 5% glucose days 1-29</p> <p>6F electrolyte soln days 1-11</p>	<p><i>Clinical signs</i> - No deaths. Distended abdomen for animals 1, 3 and 4</p> <p><i>Body weight</i> - Unaffected by treatment</p> <p><i>Food consumption</i> - Reduced for animals 2, 3 and 5</p> <p><i>Water consumption</i> - Increased for animals 4 and 5. Variable for animal 2.</p> <p><i>Biochemistry</i> - Blood urea nitrogen and creatinine ↓ for animal 4</p> <p><i>Urinalysis</i> - Volume ↓ for animals 3 and 4. pH ↑ for animal 5. Glucose ↑ for animal 4.</p> <p><i>Peritoneal fluid</i> - (for animals 3-6 only) Total protein greater in animals 3 and 6. WBC count lower for animals 3, 4 and 5.</p> <p><i>Necropsy</i> - Reddening of intestine, omentum and pancreas.</p>

**MULTIPLE DOSE STUDIES IN THE BEAGLE DOG (cont.)**

Route	Duration	No / Group ( )	Dose	Observations
IP (IRI report 7523)	28 days	(1) 4 M, 4 F (2) 3 M, 3 F (3) 4 M, 4 F (4) 4 M, 4 F  Groups 1, 3 and 4 included 1 M and 1 F for 14 day recovery period.	30 ml / kg twice daily  Electrolyte soln. 5% glucose soln. 14% icodextrin soln. 20% icodextrin soln..	<p><i>Clinical signs</i> - No deaths. Abdominal distension frequent in groups 3 and 4. Less frequent in group 2.</p> <p><i>Body weight</i> - No adverse effects attributable to treatment</p> <p><i>Food consumption</i> - ↓ in groups 2, 3 and 4</p> <p><i>Water consumption</i> - ↑ in groups 3 and 4</p> <p><i>ECG</i> - ↑ heart rate in groups 2, 3 and 4.</p> <p><i>Ophthalmoscopy</i> - No treatment related abnormalities</p> <p><i>Haematology</i> - No treatment related changes</p> <p><i>Biochemistry</i> - In groups 3 and 4 blood glucose ↑, sodium ↓, potassium ↑, alkaline phosphatase ↑.</p> <p><i>Urinalysis</i> - In groups 3 and 4 ↓ pH, volume and sodium, ↑ SG, potassium, creatinine and creatinine clearance.</p> <p><i>Peritoneal fluid</i> - ↑ in groups 3 and 4. Minimal in groups 1 and 2</p> <p><i>Necropsy</i> - Red areas, thickening and adhesions of peritoneal surfaces probably due to presence of catheter.</p> <p><i>Organ weights</i> - Adrenal weight ↑ in group 4</p> <p><i>Histopathology</i> - ↓ vacuolation and hyperplasia of zona glomerulosa in adrenals of groups 3 and 4. Recovery animals showed these findings to a lesser extent.</p> <p><i>Electron microscopy</i> - No ultrastructural abnormalities in spleen, lymph node or liver in groups 3 and 4.</p> <p><i>Recovery animals</i> - Sole abnormality was incomplete return to normal appearance of adrenal cortex.</p>

## MUTAGENICITY STUDIES

### AMES TEST

<i>Test cells:</i>	Salmonella typhimurium; strains TA 1535, TA 1537; TA 1538; TA 98; TA 100
<i>Test for induction of:</i>	Reversion to histidine independence
<i>Metabolising systems:</i>	Arochlor 1254 - induced rat liver S9 mix.
<i>Formulation of test substance and final conc:</i>	a) Icodextrin 33 to 10,000 µg per plate b) S9 mix: 0.5ml per plate
<i>Positive controls:</i>	2 Amino Anthracene, Sodium Azide, 9 – Aminoacridine, 2 - Nitrofluorene
<i>Number of independent experiments:</i>	2
<i>Number of replicate cultures:</i>	3
<i>Results:</i>	Results for dextrin were similar to those for negative control (water) both with and without metabolising system: no evidence of mutagenic activity
<i>Effects of positive control:</i>	Results were within the normal ranges expected for each bacterial strain and activation system

### CHROMOSOMAL ABERRATION ASSAY IN CHINESE HAMSTER OVARY CELLS

<i>Test cells:</i>	Chinese Hamster Ovary
<i>Test for induction of:</i>	Clastogenic activity
<i>Metabolising system:</i>	Arochlor 1254 induced rat liver (S9 mix)
<i>Formulation of test substance and final conc:</i>	In Hams F-10 medium, 25,000 to 200,000 µg per ml with S9 mix, 50,000 to 200,000 µg per ml without S9 mix
<i>Treatment and recovery time:</i>	With S9 mix - exposure period 0-6h, recovery period 6-24h Without S9 mix - exposure period 0-24h, recovery period none
<i>Positive controls:</i>	a) with S9 - cyclophosphamide 40 and 80 µg per ml b) without S9 - methyl methanesulphonate 20 µg per ml
<i>Number of independent experiments:</i>	With S9 - 4 concentrations of icodextrin      Without S9 - 4 concentrations of icodextrin
<i>Number of replicate cultures:</i>	2
<i>Number of cells analysed per culture:</i>	100, except MMS – 50
<i>Genotoxic effects</i>	In both presence and absence of S9 - no evidence of structural or numerical aberrations with icodextrin
<i>Effects of the positive control:</i>	CPH + S9 and MMS - S9 induced structural chromosomal aberrations with concentration related increase for CPH

h<sub>4</sub>

## MUTAGENICITY STUDIES

### MOUSE MICRONUCLEUS TEST

<i>Species / strain:</i>	Mouse / CD1
<i>Number of animals:</i>	20 male, 20 female
<i>Target cells:</i>	Bone marrow erythrocytes
<i>Test for induction of:</i>	Micronuclei
<i>Test substance:</i>	5%, 10% and 20% icodextrin at 30ml/kg
<i>Administration route:</i>	Intraperitoneal
<i>Treatment schedule:</i>	Single administration
<i>Sampling times:</i>	24, 48 and 72 hours after dosing - 20% group    24 hours after dosing - 5% and 10% groups
<i>Positive controls:</i>	Cyclophosphamide 80mg/kg
<i>Sampling times:</i>	24, 48 and 72 hours after dosing
<i>Number of animals per group:</i>	5 male, 5 female
<i>Number of cells analysed per animal:</i>	1000 polychromatic erythrocytes
<i>Toxic effects:</i>	No evidence of bone marrow toxicity
<i>Genotoxic effects</i>	Icodextrin devoid of micronucleus inducing potential
<i>Effects of the positive control:</i>	Substantial inductions of bone marrow micronuclei at all 3 sampling times

## REPRODUCTION TOXICITY STUDY

Route (Ref)	Duration/ Days	Species/ strain	No/Group	Dose ml/kg/day	Observations	
IP (HLS report MLB032/ 990093) (Ref 26)	Days 6 to 17 of gestation	Rat/CD	8 (1) 8 (2) 8 (3)	10 control 5 icodextrin 10 icodextrin  Dose volume fixed from day 6	<p><b>Mortalities:</b> <b>Clinical signs:</b></p> <p><b>Bodyweight/Food consumption:</b> <b>Litter responses/Fetal examination:</b></p> <p><b>Day 20 necropsy of parent females:</b></p> <p><b>Conclusions:</b></p>	<p>There were no treatment related mortalities.</p> <p>The general clinical condition of the animals remained satisfactory throughout the study. Swelling was observed at the dose sites, this effect had a higher incidence in groups dosed with 10 ml/kg/day (may have been as a result of the larger volume and consequently the increased time taken to perform the intraperitoneal injection).</p> <p>No adverse effects observed.</p> <p>At day 20 of gestation no obvious adverse effects of treatment on embryo-fetal survival or development were observed.</p> <p>No obvious macroscopic differences between the treated animals and the control group.</p> <p>Icodextrin (20% solution) administered by daily intraperitoneal injection to rats from days 6 to 17 of their pregnancy at 5 or 10 ml/kg/day (volume dose fixed at day 6), was well tolerated and no deaths occurred. There were some minor clinical signs of swelling at the dose sites. The general condition of the pregnant females was similar in all groups tested.</p> <p>The evidence from this study suggested that icodextrin had no apparent adverse effects on the developing embryo or fetus.</p>

Control = electrolyte solution

Icodextrin = icodextrin 20% in electrolyte solution

### PHARMACOKINETIC TESTS

Route	Duration	Species / strain	No. / Group ( )	Dose 30 ml / kg twice daily	Sampling	Observations
IP (IRI report 7423)  See repeat dose study	28 days	Rat Sprague Dawley	(1) 4 M, 4 F (3) 4 M, 4 F (4) 4 M, 4 F	Electrolyte soln 14% icodextrin soln 20% icodextrin soln	Blood and urine samples collected at 24h after first dose on day 1 and day 28	<i>Plasma samples:</i> Total carbohydrate in plasma from rats in groups 3 and 4 was not greater than found in group 1 rats. No elevation of individual carbohydrate components.  <i>Urine samples:</i> Large increase in total carbohydrate and individual components in samples from groups 3 and 4 compared to group 1. Recovery of total carbohydrate in urine was variable but accounted for up to 30% of the dose administered.
IP (IRI report 7523)  See repeat dose study	28 days	Dog Beagle	(1) 4 M, 4 F (4) 4 M, 4 F	Electrolyte soln. 20% icodextrin soln..	Plasma: Day 1 at predose, 1h, 5h, 10h, 24h Days 21, 28 at 5h, 24h for group 4 animals only  Urine: Days 1,21,28	<i>Plasma samples:</i> Total plasma carbohydrate increased slightly following treatment with icodextrin in all post treatment samples on days 1, 21 and 28.  <i>Urine samples:</i> For group 1 total carbohydrate excreted was generally less than 2g. Considerable increase for group 4 dogs. (15 to 106g)

## LOCAL TOLERANCE STUDIES

The viability and function of peripheral neutrophils from healthy donors and cultured human peritoneal mesothelial cells were assessed following exposure to peritoneal dialysis solutions containing glucose 1.36% and 3.86% or icodextrin 7.5% at their original pH 5.2 and with the pH adjusted to 7.3 with 1.0mM NaHCO<sub>3</sub>.

### Results

Mesothelial cell cytotoxicity - Both glucose and icodextrin solutions significantly increased the release of LDH from mesothelial cells. The effect of icodextrin was greater at pH 5.2 than at pH 7.3.

PMN viability - was not significantly affected by the fluids as measured by release of lactate dehydrogenase.

Phagocytosis - Icodextrin solution was significantly more inhibitory than glucose 1.36% for zymosan phagocytosis but significantly less inhibitory for Staph. epidermidis phagocytosis and for leukotriene B<sub>4</sub> synthesis. For all parameters tested, except LTB<sub>4</sub> generation, icodextrin was more inhibitory at pH 5.2 than at 7.3.

None of the fluids tested supported the growth of either Staph. epidermidis or Ps. aeruginosa as measured by increase in viable counts.

THP-1 human monocytic cells were examined for their capacity to release thromboxane B<sub>2</sub> in response to Zymosan A in the presence and absence of glucose or icodextrin at selected concentrations.

### Results:

Glucose 0.5% to 6% w/v inhibited thromboxane B<sub>2</sub> release from zymosan A activated and resting cells both untreated and phorbol ester treated. Icodextrin 2-16% w/v showed no inhibitory effect.

The capacity of THP-1 cells to phagocytose and kill Staph. aureus was measured. 85% of bacteria opsonised with human serum were phagocytosed by control cells. This value was reduced to 43% if the serum was complement depleted or 0% if the bacteria were unopsonised. 4% glucose did not significantly reduce phagocytosis but it was reduced to 71% by 10% icodextrin. Bacterial killing 90 min after phagocytosis varied between 85-91% and was not inhibited by either glucose or icodextrin.

The migratory capacity of THP-1 cells in a chemotaxis chamber was measured after differentiation of the cells with dibutyryl cyclic AMP. Chemotaxis in the presence of FMET-LEU-PHE was inhibited about 50% by 2% glucose or 7.5% icodextrin.

### ***PRECLINICAL STUDIES CONDUCTED IN SUPPORT OF PROPOSED INDICATION***

The efficacy of Adept has been evaluated in 2 animal models, the Rabbit Double Uterine Horn and the Rabbit Sidewall Models. Data from these studies are also published – Verco SJS et al., 2000.

A series of 4 studies has been conducted with Adept using an animal model of adhesion formation post surgery - the rabbit double uterine horn model. The results of these studies are summarised below.

In the first study (ML98-001), female New Zealand white rabbits were used. The uterine horns were exteriorized and traumatized by abrasion of the serosal surface with gauze until punctate bleeding developed. Ischemia of both uterine horns was induced by removal of the collateral blood supply. The remaining blood supply to the uterine horns was the ascending branches of the utero-vaginal arterial supply of the myometrium. At the end of surgery one of the following solutions or no treatment (control) was administered. After 7 days the rabbits were sacrificed and the percentage of the area of the horns adherent to various organs and the tenacity of the adhesions was determined.

The following solutions were used:

7.5% or 20% icodextrin      10, 15, 25, 50 or 75ml

Placebo                              10 or 75ml

The placebo was the electrolyte solution for icodextrin.

The larger volumes (25ml and greater) of icodextrin (both percentages) were highly efficacious in the reduction of adhesion formation with maximal efficacy noted after administration of 75ml of icodextrin. The smaller volumes of icodextrin and the placebo had no effect on adhesion formation.

In a second study, the efficacy of 50 ml of 2.5%, 4%, 7.5%, 10%, 15% and 20% solutions of icodextrin was evaluated. Administration of 50 ml of icodextrin in various concentrations was shown to reduce the extent, tenacity and incidence of adhesion formation. The administration of 2.5% icodextrin had reduced efficacy compared with the solutions containing 4% icodextrin or above, which gave similar efficacy regardless of concentration. No excess fluid was present at necropsy and no inflammation was associated with the administration of icodextrin.

A third study, evaluated 4% and 20% icodextrin compared with saline solution or lactated Ringers solution used during the operative procedure as a lavage and postoperatively as an instillate of 50 ml in the same animal model. As before, administration of 50 ml of icodextrin 4% as an instillate with and without icodextrin, saline or lactated Ringers solution as a lavage was shown to reduce the extent, tenacity and incidence of adhesion formation. A similar reduction was not observed after administration of saline or lactated Ringers as instillate with and without the same solution as lavage. Although the use of icodextrin solution as a lavage contributed no statistically significant additional effect on adhesion formation, a reduction in the involvement of non surgical sites was evident.

The fourth study, evaluated the administration of 50 ml of icodextrin at various concentrations in a blinded experiment using the same animal model. The results were consistent with the previous findings.

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 whilst 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 demonstrated that both products significantly reduced adhesion formation in comparison to surgical controls, with no significant difference between the two products.

### ***Rabbit Sidewall Model***

A study has been conducted to evaluate the efficacy of Adept in the reduction of adhesion formation or reformation after lysis in a rabbit model of adhesions between the sidewall and cecum and bowel.

Female, New Zealand white rabbits were used. A mid-line laparotomy was performed and the cecum and bowel were exteriorised and traumatised by abrasion of the serosal surface with gauze until punctate bleeding developed. Part of the peritoneum and transverse abdominal muscle was removed on the right sidewall. At the end of surgery rabbits were randomised to receive 50ml of 4% icodextrin solution or no treatment (control).

Seven days later, some of the rabbits from each treatment group underwent a second laparotomy and adhesiolysis was performed in rabbits where adhesions were present (following scoring). Rabbits were randomised to receive 50ml 4% icodextrin solution or no treatment (surgical controls) at the end of surgery. After 7 days the rabbits were sacrificed and the percentage of the area of the sidewall injury involved in adhesions and the tenacity of any adhesions was determined in a blinded manner.

The study showed that administration of 50ml of 4% icodextrin solution at the end of initial surgery, or after adhesiolysis, increased the number of rabbits that were free of adhesions and the extent of adhesion reformation. No excess fluid or inflammation was observed at necropsy.

A further study was conducted in the same animal model to evaluate the effect of Adept on the histological appearance of the peritoneum. The same initial surgery (without the additional adhesiolysis stage) and the same treatments were used. After 7 days the rabbits were sacrificed and the site of injury was evaluated histopathologically in a blinded manner.

The study showed the same effect of reduction in sidewall adhesions compared to controls for the 4% icodextrin treated group. Gross examination indicated no inflammation, excess fluid or gross lesions on any organs. Histopathological evaluation of the sidewall injury showed no excess inflammation and a normal healing process comparable to surgical controls (but without adhesion formation) in the icodextrin-treated rabbits.

## ***SAFETY STUDIES***

### ***Increased risk of infection - Onderdonk Animal Model***

The effect of administration of 4% icodextrin on abscess formation following intraperitoneal infection in rats has been evaluated (ML98-007 – see Volume 5). 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 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 for bacterial peritonitis.

### ***Haemolysis***

The compatibility of icodextrin with blood has been evaluated by performing an haemolysis test (direct contact method - ISO 10993-4). Icodextrin was found to be non-haemolytic.

### ***Anastomotic Healing***

#### ***Preliminary Study in Rats***

A study was carried out in rats, using either Adept or phosphate buffered saline (PBS), to determine the effects on incisional and anastomotic healing. Incisional (laparotomy) site tear strength and bursting pressure at the site of the bowel anastomosis were evaluated in a total of 27 rats (12 Adept, 15 PBS).

At time points of seven and twenty-one days postoperatively, there was no significant difference in tear strength of incisional site (laparotomy wound) between the two groups.

At day seven there was no difference in the bursting pressure required to rupture the anastomotic site between the groups.

In the Adept group, at day ten postoperatively, the pressure required to rupture the anastomotic site was approximately 50% higher than for the group treated with PBS. This difference was not significant due to the small number of animals and wide variability. However, this same difference continued to be observed at day twenty-one postoperatively, and at this time-point was significant ( $p=0.049$ ).

#### ***Full Study in Rabbits***

A full study was conducted in a rabbit model to evaluate the effect of Adept used both as a preoperative lavage and post operative instillate, on the healing of a bowel anastomotic site and a laparotomy incision. 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 a commonly used surgical solution, lactated Ringer's solution or surgery only.

Forty eight female rabbits were randomly assigned to one of three treatment groups (Surgical Control, Solution A, Solution B) and one of two sacrifice groups (post-operative day 7 or day 21) for a total of six groups with eight animals per group. The test and control materials were labelled only as Solution A or Solution B, therefore study personnel were blinded to their identity. 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.

Post operative behaviour in the animals was observed daily. At termination, adhesion and abscess formation were evaluated. Mechanical testing (bursting and tear strength) were evaluated in six animals per group. The remaining two animals per group were selected for histology and were used to assess anastomotic and incisional healing. All evaluations subsequent to necropsy were conducted in a fully blinded manner for both treatment and control groups.

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.

Therefore, this study showed that Adept has no effect on the healing of bowel anastomoses and laparotomy incisions in a rabbit model.

## **Conclusions**

Solutions of icodextrin, used as a lavage during surgery and as an instillate post-operatively, have been shown to reduce significantly the incidence of adhesions (in the absence of inflammation or excess fluid at necropsy) in the standardised rabbit uterine horn model. Optimal efficacy was achieved with concentrations of 4% icodextrin and above. The 4% solution has also been shown to reduce the incidence and extent of adhesions in the rabbit sidewall formation and reformation model.

It has been shown that icodextrin is non-haemolytic and that the 4% solution does not increase the risk of peritoneal infection nor have an adverse effect on bowel anastomotic healing or wound strength in rabbits. Thus, the solution is suitable for use during surgical procedures.

### RABBIT DOUBLE UTERINE HORN ADHESION MODEL STUDIES

Study No. (Ref)	Treatment during operative procedure	Instillation of solution at end of procedure	Results
ML98-001	None	None Placebo (electrolyte soln) - 10, 75ml Icodextrin 20% soln. - 10, 15, 25, 50, 75ml Icodextrin 7.5% soln - 10, 15, 25, 50, 75ml	Volumes of 25ml, or greater, of icodextrin produced a significant reduction in adhesion formation. There was no difference between 7.5% and 20% solutions. Lower volumes of icodextrin or placebo had no effect on adhesion formation.
ML98-002	None	None Lactated Ringers soln - 50ml Placebo (electrolyte soln) - 50ml Icodextrin soln 2.5%, 4%, 7.5%, 10%, 15%, 20% - 50ml	Solutions containing at least 4% icodextrin reduced adhesion formation.
ML98-003 + ML98-003 ext.	None None None None Lactated Ringers soln Saline Icodextrin 4% Lactated Ringers soln Saline Icodextrin 20%	None Lactated Ringers soln - 50ml Saline - 50ml Icodextrin 4% - 50ml Lactated Ringers soln - 50ml Saline - 50ml Icodextrin 4% - 50ml Icodextrin 4% - 50ml Icodextrin 4% - 50ml Icodextrin 20% - 50ml	Post-operative instillation of icodextrin reduced adhesion formation, with or without intra-operative lavage.  Although lavage with icodextrin contributed no significant additional benefit over icodextrin instillate, the incidence of non surgical site adhesions was reduced.
ML98-004	None	None Placebo (electrolyte soln) - 50ml ) Icodextrin 2.5% - 50ml ) instilled on a Icodextrin 4% - 50ml ) blinded basis Icodextrin 15% - 50ml )	Icodextrin 4% and 15% reduced the formation of adhesions.
ML98-009	None None Icodextrin 4%	None (surgical control) ) Intergel™ - 15ml ) Adhesions evaluated Icodextrin 4% - 50ml ) in a blinded manner	Icodextrin 4% and Intergel significantly reduced adhesion formation compared to surgical controls. Overall scores for incidence, extent and severity of adhesions: Icodextrin 4% : 12.8±1.7 Intergel : 9.8±1.6 Control : 23.3±1.5

**3. PRECLINICAL STUDY RESULTS (continued)**

**3.2 Responses to Questions**

The responses are provided overleaf.

14. **The submission refers to the theoretical pathway of icodextrin metabolism from removal of icodextrin from the peritoneal cavity through excretion in urine. However, it does not appear that the exact method of icodextrin metabolism is known. The device description provided in Volume 1 of the submission indicates that icodextrin is metabolized to and excreted in urine as glucose. The pharmacokinetics study conducted in dogs (Volume 6, page 232) showed that large molecular weight forms of icodextrin are present in plasma and are excreted in urine. Similarly, large molecular weights forms of icodextrin are also present in human plasma; however, this module does not contain any information on whether large molecular weight forms of icodextrin are excreted in human urine. Based on the animal studies, it would be expected that human urine would also contain large molecular weight forms of icodextrin. Please provide information on the forms of icodextrin excreted in the urine of humans with functional kidneys. In the event that large molecular weight forms of icodextrin are excreted in human urine, please provide a justification of the validity of your proposed icodextrin metabolic pathway.**

The pharmacokinetics and metabolism of icodextrin have been evaluated in man in a number of studies<sup>14)15)</sup> (Davies; Moberly) – see Appendix 5.

The structure of icodextrin is similar to that of glycogen, i.e. the glucose residues are joined largely through  $\alpha$ 1,4 links but there is a small degree of branching through  $\alpha$ -1,6 link. Glycogen has a higher degree of branching through  $\alpha$ -1,6 links.

Such starchlike carbohydrates are substrates for  $\alpha$ -amylase found in plasma. Alpha amylase readily hydrolyses these carbohydrates to disaccharides, maltose and isomaltose. The disaccharides are metabolised to glucose by specific enzymes, maltase and isomaltase found in a variety of mammalian tissues<sup>16)</sup>. Thus it was expected that icodextrin in the systemic circulation would be hydrolysed by  $\alpha$ -amylase predominantly to maltose and isomaltase which would then be metabolised to glucose to enter the body pool. If icodextrin enters cells then it would be a substrate for the enzymes of glycogen metabolism, glycogen phosphorylase and the debranching enzymes.

A number of studies<sup>17 18 19)</sup> have demonstrated the safety of intravenous infusions of dextrans with a similar molecular weight profile to icodextrin and shown that a large proportion of the dose (40-50%) was rapidly excreted unchanged in the urine. These studies showed that carbohydrates with structures similar to icodextrin are cleared from the systemic circulation by the kidneys and by metabolism to smaller fragments, eventually glucose.

Thus it would be expected that in patients with functional kidneys icodextrin and its metabolic products – a range of oligosaccharides of shorter chain length down to maltotetrose, maltotriose and maltose – would be excreted in the urine. (N.B. glucose would not be expected to be excreted in urine in man.)

The studies conducted specifically to evaluate the pharmacokinetics of icodextrin support these expectations and also the metabolic pathway provided in the device description.

To summarise:

Metabolism of Icodextrin polymers occurs to a very limited degree, if at all, in the peritoneum and after systemic absorption is controlled largely by serum amylase rapidly hydrolysing the 1-4 glucosidic linkages to produce lower molecular weight fragments and glucose. After a single intraperitoneal dose of Icodextrin in patients with limited or no renal function Moberly et al<sup>15)</sup> found that only the low molecular weight fragments DP 2-4 could be measured in the plasma significantly above baseline. Furthermore in those patients with some degree of renal function the metabolites found in the urine mirrored those that could be measured in the blood. These results suggest that Icodextrin polymers are rapidly hydrolysed to glucose which enters the standard glucose metabolism pathways, and low molecular weight polyglucose species which are excreted by the kidney.

- 15. What are the expected rates of clearance of Adept™ from the peritoneal cavity and from the body following the dosing profile to be provided in the Adept™ Instructions for Use? If these rates are determined based on humans or animal models using alternate dosing profiles, please explain how these conclusions are reached.**

A pharmacokinetic evaluation of the uptake of Icodextrin from the peritoneal cavity in renal failure patients (Moberly et al) has indicated that approximately 40% of the administered dose of Icodextrin was cleared from the peritoneum over a 12 hour period. The kinetics of the uptake from the peritoneum appeared to be at a constant zero order rate of approximately 3.3% of the dose per hour, which was believed to be consistent with the rate of lymphatic drainage. These data would imply a complete clearance of Icodextrin from the peritoneum in approximately 30 hours.

Clearance of Icodextrin from the body is largely by renal excretion of the low molecular weight (DP2-4) glucose polymers maltose, matrotriose, and maltotetrose with some glucose metabolite entering the body's normal glucose metabolism. Moberly et al determined that Icodextrin renal clearance was directly related to renal function as measured by creatinine clearance. It is possible to extrapolate from data derived from these patients with compromised glomerular filtration (median creatinine clearance of 5 ml/min) to patients with normal kidney function (creatinine clearance of approximately 100ml/min) and determine that approximately 80% of the systemically absorbed dose would be excreted by the kidneys in the 24 hours following intraperitoneal icodextrin administration.

**References**

14. DS Davies: Kinetics of Icodextrin. *Peritoneal Dialysis International*. 14, Suppl.2, 1994, S45-S50.
15. JB Moberly *et al.*, Pharmacokinetics of Icodextrin in peritoneal dialysis patients. *Kidney International* 62, Suppl.81, 2002, S23-S33.
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17. Bibby JR *et al* Intravenous infusion of a dextrin Caloreen in human subjects: metabolic studies. *Br J Nutr*. 1977; 38 351-352
18. Flores M *et al* Comparative metabolism of intravenously injected sucrose and trehalose in rats. *Comp Biochem Physiol* 1975; 50 B:221-4
19. Finke C *et al* Utilisation of maltose and oligosaccharides after intravenous infusion in man *Nutr Metab* 1977; 21 (Suppl 1): 115-17

7. **In response to Question 15 of our August 3, 2004, letter, you state that the Moberly (2002) reference indicates that peritoneal clearance has a zero order rate constant of approximately 3.3% of dose per hour. Where was this 3.3% per hour provided in the Moberly reference, or how did you calculate it?**

In Moberly et al<sup>2)</sup> median absorption of Icodextrin from the peritoneal cavity in a group of renal failure patients over a twelve (12) hour dwell time was determined to be 40.1% of the total administered dose. The range of dose absorption from the peritoneum in this group of patients was found to be 24.2 to 68.3% of the administered dose. This study could only be conducted over the twelve hour dwell time because of the limitations of the CAPD prescription in the patients but Moberly et al<sup>2)</sup> calculated that the absorption process followed zero order kinetics over this time period. On this basis the median absorption rate was  $40.1/12 = 3.3\%$  of the dose per hour with a range from 2.02 to 5.69% per hour.

8. **In your response to Question 1 of the August 3, 2004, letter, you provide a reference (Appendix 1, page 18) indicating that when 2 liters of 4% icodextrin solution was instilled in the peritoneal cavity of patients with colorectal cancer, half the instilled volume remained after 72 and 96 hours. In your response to Question 15 of the same letter, you provide a reference (Moberly, 2002, page 71 of your submission) in which 2 liters 7.5% icodextrin is administered to peritoneal dialysis patients; based on these study results, you estimate that icodextrin will be completely drained from the peritoneal cavity in approximately 30 hours.**

**Please reconcile the findings of these two studies, and provide the expected rate of clearance of Adept™ from the peritoneal cavity following the dosing profile to be provided in the Adept™ Instructions for Use with the Adept™ product's intended patient population. Please explain how this conclusion is reached.**

**Note that the Moberly paper indicates a range of rates of clearance from the peritoneal cavity. Given the likely variability among patients, please consider this information and discuss the range of the expected clearance times of Adept™.**

The clinical study conducted in patients with colorectal cancer was an opportunistic experiment in patients with indwelling catheters, which allowed estimation of residual volumes of instilled fluid after various dwell times in the peritoneum. No measure of residual Icodextrin was attempted but the study did indicate that a substantial volume of fluid remained in the abdomen of these patients 72 to 96 hours after the original administration of 2 litres of 4% Icodextrin solution. These residual volumes of fluid were significantly greater than those remaining after administration of saline solution. As indicated in the answer to question 7 resulting from the study by Moberly et al<sup>2)</sup> in CAPD patients, the initial absorption of Icodextrin from the peritoneum appears to follow zero order kinetics over at least the first twelve hours and in this study the rate of uptake of Icodextrin polymer from the peritoneum ranged from approximately 2 to 6% of the administered dose per hour.

There is no practical method for measuring the period over which complete absorption takes place when Adept™ is used as a device for adhesion reduction. However the work of Moberly et al provides an estimation of the maximum absorption rates which would equate to complete systemic absorption of the Icodextrin in a range from  $100/5.69 = 17.5$  hours to  $100/2.02 = 49.5$  hours. It could be assumed that fluid volume in the peritoneum would exceed the residence times for Icodextrin substance.

9. **In your response to Question 15 of the August 3, 2004, letter, you provide a reference (Moberly, 2002, page 71 of your submission) in which 2 liters of 7.5% icodextrin is administered to peritoneal dialysis patients. From this study, you estimate that for patients with normal kidney function, 80% of the icodextrin dose in the systemic circulation will be excreted by the kidneys in the 24 hours following intraperitoneal administration. When do you expect Adept™ to be fully cleared from the body following administration according to the Adept™ Instructions for Use with the Adept™ product's intended patient population? Please provide the expected range of times with some statistical description, where possible, and explain how these conclusions are reached.**

The study published by Moberly et al<sup>2)</sup> as indicated in the response to question 8 above, suggests that Icodextrin will be completely absorbed from the peritoneum over a period of time ranging from approximately 18 to 50 hours. These times have been derived from the fact that Moberly calculated that the constant absorption rates of Icodextrin in their patients ranged from 2 to 6 percent of the administered dose per hour and therefore 100% absorption would equate to a range between  $100/6$  and  $100/2$  hours. This absorption rate estimation would be independent of the initial concentration of Icodextrin in the administered solution and furthermore the renal status of the patients would not influence this absorption rate.

Moberly et al<sup>2)</sup> also measured the renal excretion of Icodextrin in those patients with residual renal function and found that as would be expected Icodextrin renal excretion was directly correlated with measured creatinine clearance. Since there is no apparent barrier to urinary excretion of a water soluble compound like Icodextrin under normal renal function conditions, it would be expected that renal excretion of the compound would equate to glomerular filtration rate (GFR) or approximately 100ml/min or 6 L/hour. Utilizing the systemic volume of distribution for Icodextrin of 22.7 L calculated by Moberly it is possible to estimate a half life of elimination for the compound from the systemic circulation in patients with normal renal function as would be the case in patients receiving a single dose of Adept™ during a surgical procedure using the following formula:

$$\begin{aligned} t_{1/2} &= 0.693Vd/\text{Clearance} \\ &= 0.693 \times 22.7/6 = 2.6 \text{ hours} \end{aligned}$$

The renal excretion of Icodextrin is clearly very much more rapid than the absorption from the peritoneum and therefore the absorption rate from the peritoneum will be the controlling factor in the elimination of the substance from the body. In pharmacokinetic terms it is usually assumed that 100% clearance of a compound from the body has occurred after approximately 5 elimination half lives. Therefore it could

be assumed that complete elimination of Icodextrin from the body of patients receiving the product according to the instructions for use would occur approximately 13 hours ( $5 \times 2.6$ ) after complete absorption of the product which in the slowest case might be 50 hours after treatment. Based on the absorption rates calculated by Moberly this complete elimination of Icodextrin may be accomplished 31 to 63 hours after the use of the product during a surgical procedure.

**References**

2. JB Moberly *et al.*, Pharmacokinetics of Icodextrin in peritoneal dialysis patients. *Kidney International* **62**, Suppl.81, 2002, S23-S33.
3. DS Davies: Kinetics of Icodextrin. *Peritoneal Dialysis International*. **14**, Suppl.2, 1994, S45-S50.



**Mechanism of Action, Clearance and Metabolism**

5. Numerous references were made in the PMA to the principle of action for the ADEPT® ARS as being hydroflotation of proximal surfaces following pelvic surgery. Please provide descriptive information to support this theory, including clearance time from the peritoneal cavity, wettability of the 4% icodextrin solution, and ability to adhere to tissues *in situ*.
  
6. In your response to Question 9, Module 1, Amendment 3:
  - a. You stated that there would be residual fluid accumulation in the peritoneal cavity after icodextrin had been cleared. Please provide rationale for this residual fluid accumulation and how long it will persist after icodextrin clearance. Also, please discuss whether fluid accumulation was a side-effect of icodextrin treatment or part of the device's mode of action. Finally, please provide a detailed description, including pre-clinical test results and published scientific literature, of the device's mode of action to prevent adhesion formation.
  
  - b. You estimated that ADEPT® would be cleared from the peritoneum between 18 and 50 hours after administration with total body clearance occurring between 31 and 63 hours. These calculations indicated that ADEPT® may be present in the peritoneal cavity for less than 1 day (18 hours) or potentially for just over two days. Please provide a detailed description of the progression of adhesion formation and the duration that tissue surfaces need to be separated to reduce the risk of adhesion formation, taking into account the estimated clearance rates for ADEPT®.

The following discussion is a response to both question 5 and 6.

The rationale for the evaluation of 4% icodextrin solution as an adhesion reduction agent is based on the **hypothesis** that separation of traumatised peritoneal surfaces might be achieved, by the presence of fluid during the period post surgery thought to be critical to adhesion formation.

It has been reported anecdotally that in CAPD patients the occurrence of adhesions is low even though there may be gross peritoneal damage. The view has been expressed that the constant separation of peritoneal surfaces by an adequate volume of fluid in these CAPD patients may explain the apparent lack of adhesions and thus might be a method of preventing intraperitoneal adhesions post surgery<sup>1)</sup>.

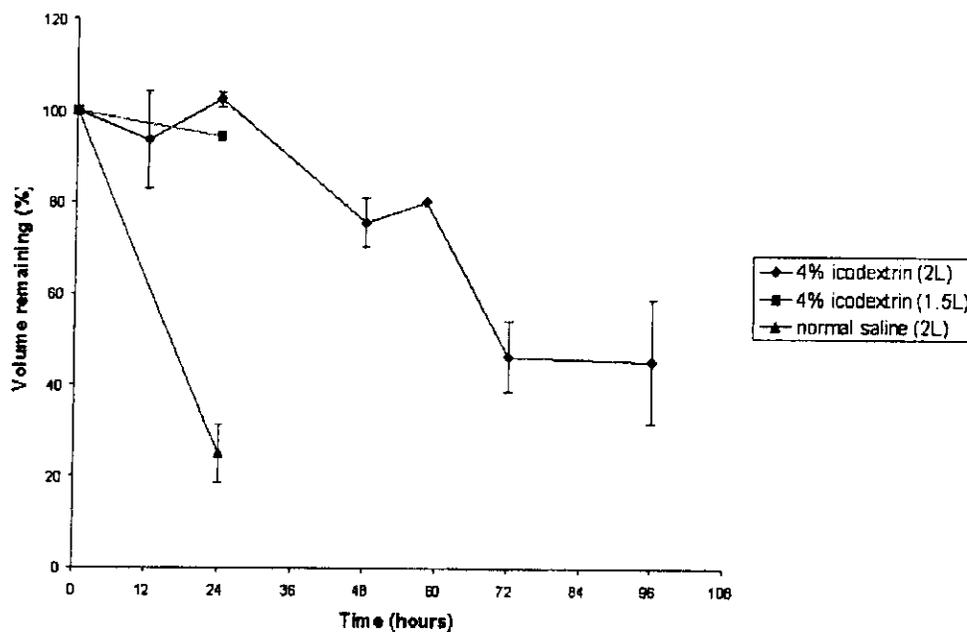
It has been demonstrated both in animals and man that icodextrin solution is able to maintain a reservoir of fluid within the peritoneal cavity for a prolonged period of time when compared to crystalloid solutions.

Preclinical studies in the rabbit uterine horn model and in the rabbit sidewall formation and reformation model (see Module 1, Volume 7) have shown that icodextrin solutions at concentrations of 4% and above are able to reduce adhesion formation compared with both surgical controls and also the equivalent volumes of Ringer's Lactate or saline. These preclinical investigations also demonstrated the prolonged residence time of icodextrin solutions in the rabbit peritoneal cavity. Distended abdomens were observed for up to 48 hours following the i.p. administration of 50ml 10%, 15% or 20% icodextrin in 1/10, 2/10 or 10/10 rabbits respectively. In a study in which the effects of volumes of 10, 15, 25 and 50 and 75ml of 7.5% or 20% icodextrin solutions were compared with 10 or 75ml of placebo or no treatment, distended abdomens were observed for 24 hours in 3/10 rabbits receiving 75ml of 7.5% icodextrin solution and for 48 to 72 hours in 8/10 rabbits receiving 75ml of 20% icodextrin solution. In contrast, distension was not observed in the animals receiving 75ml placebo (electrolyte vehicle).

These data demonstrate that icodextrin solutions maintain fluid in the abdomen for prolonged periods and are consistent with the hypothesis that the maintenance of a fluid reservoir within the peritoneal cavity in the early post operative period is the means by which adhesion formation is reduced.

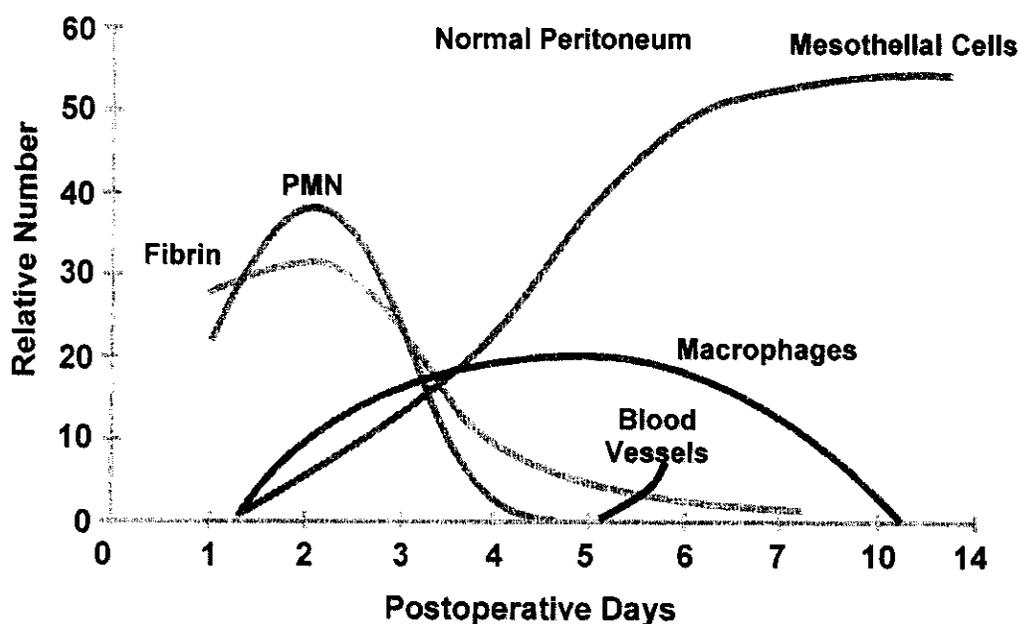
The fluid dynamics of 4% icodextrin have been evaluated in an opportunistic experiment in patients with colorectal cancer who had indwelling catheters, thus allowing the estimation of residual volumes of instilled fluid after various dwell times in the peritoneal cavity. This study demonstrated that there was negligible change in volume after 24 hours and a substantial residual volume of fluid (approximately half that instilled) remained in the abdomen of these patients 72 to 96 hours after the original instillation of 2 litres of 4% icodextrin solution<sup>2)</sup>. In contrast, in patients who had 2 litres of saline or 1.36% glucose solutions instilled, the volume after 24 hours was reduced by approximately 75%.

Change in intraperitoneal fluid volume over 96 hours  
[mean +/- s.e.m.] Fluid volume remaining



The processes that lead to either normal peritoneal re-epithelialization or the formation of fibrous adhesions have been extensively investigated (3-13). Adhesion formation typically occurs when two injured peritoneal surfaces are apposed. The initiation of adhesion formation begins with formation of a fibrin matrix, which usually occurs during coagulation within the surgical procedure or over the next 36 hours as a result of tissue response to surgical trauma (6,7)

Figure 1: Change in Relative Number of Cellular Elements



diZerega GS and Rodgers KE. The Peritoneum, Springer Verlag, New York, 1992, page 299

Surgical injury of tissue reduces or eliminates blood flow, thereby producing ischemia, which leads to local persistence of fibrin matrix. In addition, blood clots are slow to achieve complete organization over the first 12-24 hrs after surgery further contributing to the build up of fibrin matrix within the pelvis (10,11). Initially, this matrix consists of strands or condensed masses of fibrin that are sticky. When the fibrin matrix comes in contact with adjacent pelvic surfaces it can form a fibrin bridge interconnecting the two surfaces (10,13). Thus, fibrin matrix attaching to tissue surfaces is a necessary precursor for adhesion formation. Mobile intraperitoneal structures will not permanently adhere to each other unless held in continuous, close apposition by the fibrin bridge until fibroblast invasion leads to collagen deposition, beginning 36 to 48 hrs after surgery (8-10) see Figure 1 above. Thus, the crucial consideration that determines whether the fibrin bridge is absorbed, or persists and is organized, is the intrapelvic environment following surgery. Preventing fibrin bridge formation during this time will result in reduced adhesion formation (10,12,13).

The kinetics of peritoneal adhesion formation using permanent barriers to tissue apposition also indicate that susceptibility for adhesion formation is significantly decreased after the first 36-48 hours after surgery (12). Evaluation of antiadhesion agents showed that the magnitude of adhesion prevention was directly proportional to the agent's ability to remain at the site of injury during this critical period following surgery. An agent that remains on injured surfaces for at least 36 hours after peritoneal injury is more effective in reducing adhesion formation than an agent with a shorter residence time (12).

The efficacy of antiadhesion agents such as films and gels may therefore be related to their ability to adhere to the tissue surface in addition to their residence time at the site of injury. However, in the case of Adept, its wettability or ability to adhere to tissues would be expected to be of no significance. Instead, its ability to remain in situ, facilitating the mobility of intraperitoneal structures and minimising the ability of

injured tissue surfaces to remain in permanent close apposition, is proposed as being fundamental to its mode of action. Nevertheless, as requested at a meeting with the agency on August 16<sup>th</sup>, the surface tension of Adept and Ringer's Lactate solutions has been measured, using the Du Nouy ring method with the following result (see also Appendix 4).

Surface Tension mN/m		
Adept Solution	Lactated Ringer's Solution	Water
68.484	67.385	72.224

**In summary**, the hypothesis that adhesion reduction is achieved by facilitating the separation of peritoneal surfaces by the presence of a volume of fluid during the 36 to 48 hour period post surgery critical to adhesion formation is supported by the following data:

#### ***Preclinical***

- Solutions of icodextrin at a concentration of 4% and above were shown to be efficacious in reducing adhesion formation in the rabbit uterine horn and rabbit sidewall models.
- In a blinded study (ML98-004) 50ml of placebo and 2.5% icodextrin solutions reduced adhesion formation compared to surgical controls but to a lesser degree than the reduction produced by 50ml 4% or 20% icodextrin solutions.
- Adhesion reduction was increased by increasing volumes of 7.5% and 20% icodextrin solutions.
- Prolonged residence time in the rabbit peritoneal cavity was shown by the presence of abdominal distension in icodextrin treated animals as compared to placebo treated animals or surgical controls.
- Studies relating to the processes leading to adhesion formation.

#### ***Clinical***

- Absence of adhesions in patients on CAPD.
- Residual fluid volume drained from the peritoneal cavity of patients at intervals following the instillation of 4% icodextrin solution compared to saline or 1.36% glucose solution.
- The double blind randomised PAMELA clinical study has demonstrated significantly greater adhesion reduction post surgery for Adept treated patients compared to those receiving the same volume of Ringer's Lactate solution.

### How does Adept maintain a reservoir of fluid?

The concept of osmotic flow occurring dependent on the magnitude of an osmotic gradient is valid only across an 'ideal' semipermeable membrane. Most biological membranes are partially permeable to solutes and the direction of the osmotic force is determined by the differences across the membrane in the sum of the products of the reflection coefficients and molar concentrations rather than the total osmolality gradient (see also question 50). Osmotic flow is thus possible between solutions of similar osmolality when separated by a membrane such as the peritoneal membrane which is permeable to solutes. This "colloidal" osmotic flow is the physiological basis for fluid transport across the capillary wall and the proximal tubules in the kidney.

Early clinical studies during the development of icodextrin for CAPD demonstrated differential rates for transperitoneal oligosaccharide absorption – those with chain length less than 12 glucose units (molecular weight <2000) were rapidly absorbed (70-80% over the course of a 6 hour dwell) – those greater than 12 glucose units were poorly absorbed. This work also demonstrated that solutions of icodextrin instilled into the peritoneal cavity were capable of producing sustained ultrafiltration (i.e. removal of water and low molecular weight solutes from the bloodstream into the peritoneal cavity) despite being hypo-osmolar relative to serum. Icodextrin was thus shown to achieve its ultrafiltration effects by a process of colloidal osmosis (see also question 50).

The majority of all molecules in batches of icodextrin have a molecular weight >2000 (94% is  $\geq$  MW 1638) and therefore will not be rapidly absorbed by diffusion across the peritoneal membrane. Thus, following instillation of Adept into the peritoneal cavity, water and low molecular weight solutes will be drawn in from the blood stream by colloidal osmosis. Metabolism of icodextrin within the peritoneal cavity has been shown to be minimal and therefore the instilled icodextrin will be cleared slowly from the peritoneal cavity at a rate limited by lymphatic drainage. Therefore, with respect to **fluid volume**, the dynamics are – the tendency to an increase in volume as a result of colloid osmosis – in parallel with removal of fluid by lymphatic uptake and other processes. Adept is thus capable of maintaining a reservoir of fluid within the peritoneum and clinical data suggest only minimal net increase in fluid volume over a period of 24 hours followed by a gradual decline with fluid remaining in the peritoneal cavity for the critical 36 to 48 hour period.

With respect to **icodextrin**, as stated previously in response to question 9 Module 1 amendment 3, there is no practical method for measuring the period over which complete absorption of icodextrin takes place when Adept is used as a device for adhesion reduction. The study by Moberley in CAPD patients indicates that the initial absorption of icodextrin appears to follow zero order kinetics over the first 12 hours with uptake ranging from 2 to 6% of the administered dose per hour. Extrapolating from these data, obtained over a 12 hour period and **assuming that absorption continues to follow zero order kinetics** beyond 12 hours, we have estimated the complete systemic absorption of icodextrin in a range from **18 to 50 hours**. However, of greater relevance to the mechanism of action of **ADEPT** are the residual volumes measured over a period of 96 hours<sup>2)</sup>.

**References:**

1. Dobbie JW. Separation of peritoneal surfaces through the maintenance of an artificial ascites as a preventative of peritoneal adhesions. 4<sup>th</sup> Int Congress Peritoneal Tissue Repair 16-19 Sep 1997; Göteborg, Sweden. Abstract from peritoneum and peritoneal Access Meeting.
2. Hosie K, Gilbert JA, Kerr D, Brown CB, Peers EM. Fluid dynamics in man of an intraperitoneal drug delivery solution: 4% icodextrin. *Drug Delivery* 2001, 8:9-12.
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6. Lamont PM, Menziens D., Ellis H. Intra-abdominal adhesion formation between two adjacent deperitonealised surfaces. *Surg Res Commun* 13:127-130, 1992
7. Haney AF, Doty E. The formation of coalescing peritoneal adhesions requires injury to both contacting peritoneal surfaces. *Fertil Steril* 61:767-775,1994
8. Ellis H. The cause and prevention of postoperative intraperitoneal adhesions. *Surg Gynecol* 133:497-511, 1971
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10. Buckman RF., Buckman PD, Hufnagel HV., et al. A physiologic basis for the adhesion-free healing of deperitonealized surfaces. *J Surg Res.* 21:67-76,1976
11. Bridges JB, Johnson FR, Whitting HW. Peritoneal adhesion formation. *Act Anat (Basel)* 261:203-212, 1965
12. Harris ES, Morgan RF, Rodeheaver GT . Analysis of the kinetics of peritoneal adhesion formation in the rat and evaluation of potential antiadhesive agents, *Surgery* 117: 663-9, 1995
13. DiZerega GS. Peritoneum, peritoneal healing, and adhesion formation, in *Peritoneal Surgery*, diZerega et al (eds), Springer Verlag, NY, pg 17-22, 2000

- 33. Please provide information that demonstrate that lymphatic drainage in continuous ambulatory peritoneal dialysis (CAPD) patients was comparable to that of ADEPT® patients in the intended population, (see question #6 above).**

Lymphatic drainage has been studied extensively in CAPD patients; however, in contrast we are not aware of any studies in the published literature which address this specific issue in patients undergoing gynaecological surgery.

Several physiological factors have been shown to affect the rate of lymphatic absorption from the peritoneal cavity in animal studies, including intraperitoneal fluid volume, intraperitoneal hydrostatic pressure, rate and depth of respiration, posture, intestinal peristalsis, patency of the diaphragmatic and mediastinal lymphatics and lymphatic vessel outflow pressure.<sup>1)</sup>

By comparison to 1L of Adept in the intended population, the larger volume of fluid – typically 2L – continuously present in the peritoneal cavity during CAPD ensuring constant contact of fluid with the lymphatic stomata in the sub-diaphragmatic peritoneum, together with a relatively increased intraperitoneal pressure, will tend to enhance the rate of lymphatic drainage. The influence of all other physiological factors would not be expected to differ between the two patient populations.

**References:**

1. R A Mactier & R Khanna, Peritoneal Lymphatics. The Textbook of Peritoneal Dialysis p115-134, 1994, Kluwer Academic Publishers.



Confidential PAMELA ML/AD 002

Final version 28 February 2005

### 10.5 Outcome of video audit and review process

The independent blinded video auditor audited a selection of videos, the process is described in detail in section 16.1.12. Briefly; all investigators had their first three patients' videos audited. A video was deemed to be unacceptable if it had more than three queries, defined as significant by the auditor or at the auditor's discretion. The investigators had the final decision regarding the scoring and any changes agreed upon were amended in the CRF. Once an investigator had had three "acceptable" sets of videos their subsequent videos were audited on a random (1:5) basis. In the event that an investigator's videos were found to be "unacceptable" all of the investigator's subsequent videos were audited until they had completed three consecutive sets of "acceptable" videos. Of all videos received for first and second look laparoscopies (856), 412 (48%) were reviewed, 108 (13%) had queries and 18 (2%) had unacceptable queries. All video queries were raised with the individual investigators and were answered and resolved to the satisfaction of the independent auditor. A by center breakdown is given below in Table 10.5.1

Table 10.5.1 Videos reviewed and queried per center

Site Number	Number of Videos received from the site	Number of Videos reviewed	Number of videos with queries	Number of unacceptable queries
1	137	59	10	1
2	145	64	18	3
3	44	24	9	3
4	41	23	11	3
5	17	11	4	1
6	119	28	3	0
7	67	37	10	1
8	1	1	0	0
9	24	22	2	0
10	37	22	7	0
11	63	20	4	0
12	35	16	4	1
13	25	17	7	4
14	35	20	7	0
16	42	24	5	0
18	24	24	7	1
<b>Total (%)</b>	<b>856</b>	<b>412 (48%)</b>	<b>108 (13%)</b>	<b>18 (2%)</b>

**PREMARKET APPROVAL APPLICATION**  
**SUBMISSION TO FDA**  
**FOR**  
**ADEPT™**  
**SPONSOR PANEL PACK**  
**P050011**  
**VOLUME 4 SECTIONS 6 - 7**

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Innovata PLC

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104A West Street  
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GU9 7EN  
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*Name of sponsor's agent*  
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USA

Tel: (508) 393 3100

**February 2006**

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## 6. CLINICAL STUDY RESULTS OUTSIDE U.S. STUDIES

### 6.1 ARIEL Registry Manuscripts

Data is provided overleaf.

The following documents may be viewed in the public reading room at:

Division of Dockets Management  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

C. Sutton, L. Minelli, E. Garcia, M. Krell, J. L. Pouly, G. Pados, A. M. Crowe, L. W. J. Osborne, A. D. Knight, Use of icodextrin 4% solution in the reduction of adhesion formation after gynaecological surgery

Draft: D. Menzie, M. Hidalgo Pacual, MK Walz, J J Duron, F Tonelli, A Crowe, A Knight, Use of icodextrin 4% solution in the prevsion of adhesion formation following general surgery: experience from the multicentre ARIEL Registry



**6. CLINICAL STUDY RESULTS OUTSIDE U.S. STUDIES (Continued)**

**6.2 Commercial Use Outside US**



**6. CLINICAL STUDY RESULTS OUTSIDE U.S. STUDIES (Continued)**

**6.2 Commercial Use Outside US**

**6.2.1 Approval Status of Adept in Markets Outside US**

Data is provided overleaf.

- 3b. Please state the length of time ADEPT® ARS has been approved in each of the countries where it is marketed as an adhesion barrier. Please identify the number of patients treated with ADEPT® as an adhesion reduction solution. Also, please provide some descriptive information on the AE reporting requirements in each these countries. Clarify if these reports address the amount of ADEPT® ARS used for a particular patient. If so, please provide information on the amounts used.**

Table 3 overleaf shows the dates of approval and launch in those countries where Adept is currently marketed.

Based on the assumption of 2 x 1L bags or 1 x 1.5L bags, the number of patients treated with Adept to June 2005 is 113,114, the latest date for which figures are available.

Reporting requirements for adverse events in the EU are provided in the guidance document in the following pages.

In order to fulfil the device vigilance guidelines the manufacturer is responsible for ensuring the guidelines are known to their authorised representatives, third parties responsible for marketing the device and to any other authorised agents acting on behalf of the manufacturer for device vigilance related purposes. The competent authorities should encourage the spontaneous reporting of adverse incidents by the user and other professionals. Such reports can be sent directly to the manufacturer or via a user reporting system to the appropriate competent authority.

These guidelines are followed by our licensee in all countries where Adept is marketed. France, Hungary, Luxembourg and Israel require in addition to be informed of events occurring outside their borders.

The data base of events held by our licensee is therefore a comprehensive list of any events reported spontaneously of which they become aware in addition to those reported via ARIEL.

Because the reports are spontaneous they may not always provide details of the amount of Adept used for a particular patient in spite of careful follow up. However, the labelling for Adept in all countries is the same.

TABLE 3

Country	Notes	1 Litre		1.5 Litre	
		Registration	Launch	Registration	Launch
Austria	Recognised the EU CE mark. No notification required.	-	-	Not required	Dec 2002
Belgium	Recognised the EU CE mark. No notification required.	-	-	Not required	Launch via mailing Oct 2002
Bulgaria	Recognised the EU CE mark but national authorisation was still required.	01 Aug 2003	-	01 Aug 2003	June 2004
Cyprus	Recognised the EU CE mark. No notification required.	Not required	May 2002	Not required	2003
Czech Republic	Did not recognise the EU CE mark but aided Czech conformity assessment.	-	-	31 Oct 2003	May 2004
Denmark	Recognised the EU CE mark. No notification required.	-	-	Not required	Oct 2002
Estonia	Recognised the EU CE mark. Also notified Estonian authority.	-	-	04 Jun 2003	May 2004
Finland	Recognised the EU CE mark. No notification required.	-	-	Not required	Oct 2002
France	Recognised the EU CE mark.		18 Feb 2002	Oct 2002	2003
Germany	Recognised the EU CE mark. No notification required.	Not required	Sold product Mar 2002	Not required	2003
Greece	Recognised the EU CE mark. No notification required.	Not required	May 2002	Not required	Jan 2004
Hungary	Recognised the EU CE mark.	-	-	Not required	May 2004
Ireland	Recognised the EU CE mark. No notification required.	Not required	Selling Apr 2002	Not required	2003
Israel	Recognised the EU CE mark. Notification required.	22 Mar 2002	May 2002	Based on 1L licence	Keeping 1L
Italy	Recognised the EU CE mark. Notification not required for 1.5L as covered by initial notification where no size mentioned.	29 Nov 2001	04 Dec 2001	Not required	2003
Latvia	EU CE mark aided registration.	27 Jun 2003	-	27 Jun 2003	June 2004
Lithuania	EU CE mark aided registration.	-	-	23 Jun 2003	May 2004
Luxembourg	Recognised the EU CE mark. No notification required.	-	-	Not required	2003

<b>Country</b>	<b>Notes</b>	<b>1 Litre</b>		<b>1.5 Litre</b>	
		<b>Registration</b>	<b>Launch</b>	<b>Registration</b>	<b>Launch</b>
Netherlands	Recognised the EU CE mark. No notification required.	-	-	Not required	Launch via mailing Oct 2002
Norway	Recognised the EU CE mark. Notification of Norwegian company performed.	-	-	Oct 2002	Oct 2002
Poland	Recognised the EU CE mark. Still needed Polish assessment.	-	-	31 Jul 2003	May 2004
Portugal	Recognised the EU CE mark. No notification required.	-	-	Oct 2002	Oct 2002
Slovak Republic	Did not recognise the EU CE mark but aided local assessment.	-	-	11 Sep 2003	June 2004
Slovenia	Joined EU 01 May 2004 and CE mark was recognised.	-	-	02 May 2004	Planned Sep 2004
Spain	Recognised the EU CE mark. Notification required.	31 Dec 2001	Mar 2002	Oct 2002	2003
Sweden	Recognised the EU CE mark. No notification required.	-	-	Not required	Oct 2002
Switzerland	Recognised the EU CE mark. No notification required.	-	-	Not required	Oct 2002
Turkey	Discussions with MOH ongoing – accept EU design dossier	-	-	On hold	
UK	Recognised the EU CE mark. Notification to MDA required post BSi approval.	19 Oct 1999	June 2000	BSi approval 24 Sep 2002 MDA notified 26 Sep 2002	Oct 2002



**6. CLINICAL STUDY RESULTS OUTSIDE U.S. STUDIES (Continued)**

**6.2 Commercial Use Outside US**

**6.2.2 Instructions for Use in Non-US Countries**

Data is provided overleaf.

- 3d. Please confirm that the instruction for use of ADEPT® in this PMA is the same as that used in foreign countries, i.e., used as an intraoperative wash during surgery, followed by a 1-liter (but not more than 2-liter) instillate after surgery, before closure.**

The instruction for use of Adept in the PMA, i.e. use as an irrigant during surgery and a 1L instillate after surgery, before closure, is the same in all countries where the product is marketed. A copy of the Instruction for Use leaflet is provided overleaf.



## INSTRUCTIONS FOR USE LEAFLET

**MANUFACTURER:**

Innovata plc  
Ruddington, Nottingham,  
NG11 6JS, UK

**DESCRIPTION**

ADEPT® is a single use, sterile, clear, colourless to pale yellow fluid for intraperitoneal administration containing icodextrin at a concentration of 4% w/v in an electrolyte solution.

Each 1 litre of solution contains:

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

Theoretical osmolarity 278 milliosmoles per litre

Ionic composition (approximately) per litre:

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 either 1 litre or 1.5 litres of solution.

**INDICATIONS**

ADEPT is intended for use as an intraperitoneal instillate for the reduction of adhesions following abdominal surgery, and should be used as the irrigant during the course of that surgery.

**ACTIONS**

ADEPT performs its function through a physical effect by providing a temporary separation of peritoneal surfaces by hydroflotation. This minimises tissue apposition during the critical period of fibrin formation and mesothelial regeneration following surgery, thereby providing a barrier to adhesion formation.

Icodextrin is an  $\alpha$ -1,4-linked glucose polymer which, when administered intraperitoneally as a 4% solution, is capable of maintaining a reservoir of fluid within the peritoneal cavity for up to 3-4 days. A 7.5% solution of icodextrin has been used extensively on a daily basis as a peritoneal dialysis solution for the treatment of chronic renal failure.

When given intraperitoneally, the polymer is largely retained within the peritoneal cavity. Some absorption occurs from the peritoneum into the systemic circulation where it is metabolised by amylase to smaller oligosaccharides, ultimately maltose and by maltase to glucose.

ADEPT has been shown to reduce significantly the incidence, extent and severity of post surgical adhesions in animal models (rabbit double uterine horn and rabbit sidewall models) when used as a lavage during surgery and as an instillate post-operatively.

**CONTRAINDICATIONS**

ADEPT should not be used in patients with a known allergy to starch based polymers or in patients with maltose or isomaltose intolerance.

**PRECAUTIONS****Use in Children**

ADEPT is not recommended for use in children.

**Pregnancy and Lactation**

There are limited data available from animal studies on the effects of icodextrin on reproduction or lactation and therefore ADEPT should not be used during pregnancy or lactation.

Women of childbearing potential should be treated with ADEPT only when adequate contraceptive precautions have been taken.

**Interactions with Other Medicaments**

The primary intended function of ADEPT is not to administer medicinal products. However, the bag has an injection port, which may be used for administration of drugs, if required.

A range of antibiotics, including vancomycin, cephalosporins, ampicillin, flucloxacillin, ceftazidime, gentamycin and amphotericin, have shown no evidence of incompatibility with ADEPT.

**UNDESIRABLE EFFECTS**

Undesirable effects are those typically seen following surgery. In patients receiving icodextrin 7.5% solution as part of a peritoneal dialysis regimen and on multi therapy, there have been common reports of skin reactions, including rash and pruritus. Occasionally these rashes have been associated with exfoliation.

There have been rare reports of hypersensitivity reactions in patients treated with Adept.

There have been rare reports of vulval oedema following the administration of ADEPT. The reaction generally resolves spontaneously within a few days. Oedema is a recognised event associated with the use of fluids for irrigation and instillation in laparoscopic surgery.

**DIRECTIONS FOR USE**

ADEPT is administered into the peritoneal cavity during abdominal surgery, being used as an irrigant solution during the course of surgery. Once the surgeon has completed the surgical procedure(s) and removed all packs and sponges, the cavity is aspirated of all remaining fluid. A final volume of at least 1 litre of ADEPT is then introduced into the cavity before closure of the cavity/removal of the scope.

ADEPT should be warmed to approximately body temperature prior to use, using a device specifically intended for warming solutions in operating theatres. ADEPT can be kept in a warmer at 37°C for up to 14 days, provided it is not removed and then replaced. At all other times, storage below 4°C or above 30°C is not recommended.

Using standard operating room technique:

1. Remove the outer wrap from the ADEPT bag and hang the sterile bag of solution on a stand.
2. Remove the twist-off tab from the spike port and insert a standard giving set for connection to a laparoscope or a giving set for dispensing the solution directly into the abdominal cavity in the case of laparotomy.
3. 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), or it can be dispensed into a sterile basin and applied using a syringe and cannula.
4. When used as an intra-operative irrigant solution, at least 100 mls of ADEPT should be introduced to the cavity every 30 minutes.
5. Remove remaining fluid before introducing the final instillation.
6. For the final instillation of ADEPT, prior to closure of the abdominal cavity or removal of the laparoscope, at least one litre (a new bag of ADEPT if 1 litre bags are being used) should be used. Direct the solution at the operative sites in the first instance, the remainder being distributed throughout the cavity.
7. Dispose of the bag and any unused portion of the solution following normal operating room biological hazard procedures.

**PRECAUTIONS FOR USE**

ADEPT must be used as directed by a physician. It must not be used unless the solution is clear and the container undamaged.

Any unused portion of solution should be discarded. ADEPT is not to be used for intravenous infusion.

**STORAGE**

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

**PRESENTATION**

ADEPT is packaged in single use, flexible polyvinylchloride bags, fitted with connecting ports, containing 1 litre or 1.5 litres of solution. The product is presented sterile (by heating in an autoclave). The bags are packaged in cartons of 10 x 1 litre or 5 x 1.5 litres.

ADEPT is a Registered Trade Mark of Innovata plc

Date issued: September 2005

innovata plc

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**6. CLINICAL STUDY RESULTS OUTSIDE U.S. STUDIES (Continued)**

**6.2 Commercial Use Outside US**

**6.2.3 Post-marketing Clinical Data – ARIEL Registry**

Data is provided overleaf.

### 6.2.3 Post-marketing clinical data: ARIEL Registry

Since its launch onto the UK market and subsequently other European markets, a registry (ARIEL) was set up in Europe to enable a continuous evaluation of in-practice use of ADEPT.

An independent panel of gynaecologists and general surgeons designed the method used to capture the clinical experiences. Centres were recruited on the basis of their beginning to use Adept as part of routine surgery. Each centre was provided with a "Starter Pack" which explained the purpose, methodology and blank forms. Individual gynaecologists and general surgeons were provided with these 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. The forms were available in English, French, German, Italian and Spanish.

Completed ARIEL forms were collected, mainly through the local office of the licensee, Shire, and sent to the UK for centralised processing. A standard handling and data entry/data query procedure was implemented to process the submitted forms.

A total of 4620 patients (2882 gynaecology and 1738 general surgery) at 253 centres were enrolled in the registry over a period of approximately 3 years between February 2000 and December 2003. The centres were in the UK (127), France (33), Germany (36), Spain (33), Italy (22) and Greece (2).

The range of European countries contributing patients to the ARIEL registry would be expected to cover a wide range of ethnic groups not dissimilar from those in the US. It would not be anticipated, nor is there any evidence from the now widespread use of icodextrin in Europe, USA, South America, Japan and Asia, in the renal indication that the absorption metabolism or excretion of icodextrin is affected by demographic characteristics. We are therefore not aware of any reason to assume that the European use of Adept would not be representative of the US experience.

Further details of the ARIEL Registry are provided below (taken from response in Amendment 5):

#### 6.2.3.1 Registry Protocol

##### (i) Objectives

The ARIEL Registry was initiated to capture the clinical experiences of surgeons in the routine use of Adept in a systematic way during general and gynaecological surgery. It was conceived and designed with an independent panel of gynaecological and general surgeons. Key surgical opinion leaders were identified in each country with input from the independent panel to act as National Registry Coordinators and were involved in finalising the registry. Before the registry was formally initiated small pilots were undertaken with the advisers to assess what feedback it was ethical and reasonable to expect surgeons to be able to provide from routine use of the agent. Key to this process was the ethos that this registry would allow Adept users to monitor and share their experiences. This included assessment of optimal methods of use – something that proved useful early on, for example how best to instill Adept in open and laparoscopic surgery. Via surgeon feedback, the Registry also collected

patients' perspectives on the use of the product and monitored for adverse events.  
**N.B. it was not a substitute for local Regulatory safety reporting requirements.**

The information provided through the Registry was anonymised with the contributing surgeon alone being aware of which patients' information was provided – thus allowing for follow-up if required.

At the time of registry initiation Adept was already licensed for use in Europe and surgeons in participating countries were using it as part of routine adhesion reduction practice. Ethics committee approval to participate in the registry was consequently not required (although some centres notified their local committees) and there was no specific requirement for patient consent for use of Adept or for the surgeon to provide anonymised feedback to the Registry. The consent the patient gave for surgery was sufficient. Some surgeons advised their patients that they were going to use Adept as part of an adhesion reduction strategy as part of their own good clinical practice in advising patients of potential risks of postoperative adhesions.

All participating surgeons were provided with background information in the form of a Starter Pack which acted as a protocol for the registry, this included:

1. ARIEL Purpose, Process and Practice – see Starter Pack –UK sample
2. Adept Product information – Instructions for use
3. ARIEL Summary demography – slides showing basic information as per sample from 2003
4. ARIEL Forms x 30 – Gynaecology or General Surgery as relevant – see UK sample

All materials including data collection forms were translated to provide materials in English, French, Germany, Italian and Spanish. As the two Greek centres contributing were fluent in English there was no requirement for Greek Translation.

## (ii) Site selection and recruitment of patients

As illustrated below, a total of 253 centres (150 gynaecological surgery centres and 103 general surgery centres) in France, Germany, Greece (gynaecology only), Italy, Spain and the UK contributed 2882 gynaecological patients and 1738 general surgery patients to ARIEL.

**Number of contributing centres and patients**

Country	Number of Contributing Centres	Gynae Centres	Gynae Patients	Gen Surg Centres	Gen Surg Patients
UK	127	77	1401	50	902
France	33	19	234	14	141
Germany	36	19	289	17	167
Spain	33	16	382	17	440
Italy	22	17	458	5	88
Greece	2	2	118	NA	NA
<b>TOTAL</b>	<b>253</b>	<b>150</b>	<b>2882</b>	<b>103</b>	<b>1738</b>

**(iii) Patient demographic characteristics**

During the original piloting and development of the Registry the surgical advisers and Joint European co-coordinators of the ARIEL Registry requested that height and weight of the patients in the registry should be retained by each physician on a separate form to be held by the investigator in case of follow-up. The only demographic descriptor recorded on the questionnaire form provided for analysis was age. Nevertheless the range of countries contributing patients would be expected to cover a wide range of ethnic groups not dissimilar from those in the US.

An analysis of age for all patients, for those without adverse events, for those with adverse events and for those with adverse events considered to have a causal relationship to use of Adept, are presented in the table below.

	Age (yr) Mean $\pm$ SD							
	Gynaecological surgery				General surgery			
	N		N		N		N	
	Laparoscopic	Open	Laparoscopic	Open	Laparoscopic	Open	Laparoscopic	Open
ALL	2028	35.18 $\pm$ 9.14	758	42.23 $\pm$ 12.24	254	49.40 $\pm$ 17.32	1396	59.97 $\pm$ 17.86
-Non AEs	1905	35.13 $\pm$ 9.18	681	42.01 $\pm$ 12.01	223	48.17 $\pm$ 17.36	1083	58.63 $\pm$ 18.05
-ALL AEs	123	35.98 $\pm$ 8.57	77	44.13 $\pm$ 14.04	31	58.26 $\pm$ 14.46	313	62.84 $\pm$ 16.80
-Causal AEs	41	33.66 $\pm$ 6.07	23	36.17 $\pm$ 7.46	6	53.49 $\pm$ 16.66	51	60.13 $\pm$ 16.04

As expected, the mean age of patients was lower in the gynaecological cohort than the than the general surgery cohort and was also lower in each of the corresponding laparoscopic subgroups compared to the open surgery subgroups.

**(iv) ARIEL Registry Forms**

The forms used for both gynaecological surgery and general surgery are shown overleaf.

**Sample of ARIEL Gynaecological Registry Form**

**'ARIEL'**  
**Adept Registry for clinical Evaluation**  
**GYNAECOLOGY REGISTRY**

**PATIENT DETAILS FORM**

Hospital:	<input type="text"/>	Consultant Surgeon:	<input type="text"/>
Operating Surgeon:	<input type="text"/>	Grade:	<input type="text"/>
Date of Operation:	<input type="text"/>	Patient Hospital No.:	<input type="text"/>
Patient initials:	<input type="text"/>	ARIEL Code:	<input type="text"/>
Date of birth:	<input type="text"/>	Weight:	<input type="text"/> kg    Height: <input type="text"/> m

**NOTE**

Allergies:  Yes     No

If 'yes'    Starch/Starch based Polymers-do not use ADEPT    Maltose/isomaltose-do not use ADEPT

Other (no contraindication for ADEPT) please detail

**NOTE IN COMPLETING THE ARIEL REGISTRY FORM**

Contributing surgeon to complete, detach and hold patient identifier information. This will enable you to verify queries and allow for subsequent audit of outcomes with your own patients.

Please ensure all fields on this Patient Details Form and the attached ARIEL Registry Form are completed before the Registry Form is submitted. If fields are not complete please detail why information is not available.

Please ensure writing is easily legible. Use of upper case may be helpful.

NB - Only complete forms fulfilling agreed criteria will be eligible for the Registry and analysed.

**NOTE**

Please detach this Patient Details Form

Please copy the attached Registry Form

Keep the original Registry Form with this Patient Details Form

Send the copied Registry Form to:

Prof. Sutton, ARIEL Co-ordination Group, c/o Alison Crowe, PO Box 155, UCKFIELD, TN22 4UA, UK

**Do not** send the Patient Detail Form

If you have any queries contact Alison Crowe +44 (0) 1825 733057 or Alastair Knight +44 (0) 208 891 1848

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**POST DISCHARGE OBSERVATIONS**

Please record any observations/problems from post-discharge liaison

**ADVERSE EVENTS DURING AND POST SURGERY**

Shire have a statutory responsibility for reporting any Adverse Events. It is therefore imperative that if any occur that you complete the details on the form according to the scoring below and submit this form within 24 hours to allow for Shire to process and follow-up with you as needed.

Therefore:

1. Please list any adverse events that occurred during or post surgery and their relationship to ADEPT if any as per following score: **1-unrelated; 2-unlikely to be related; 3-possibly related; 4-probably related; 5-definitely related**
2. Please consider if these events were serious and if so please rate according to the following score:  
**A serious adverse event** is one which has led to: **A** - death; **B** - a life threatening illness or injury; **C** - permanent impairment of body function; **D** - a condition necessitating medical or surgical intervention to prevent impairment. If you do not feel the event was serious as defined then score as **N**.
3. Please also consider if the use of Adept may have contributed to the event according to the following:  
**M** – malfunction of Adept; **L** – labelling of Adept; **P** – deterioration in performance (extent of adhesion reduction or re-formation) of Adept, as assessed by comparing initial versus second-look (if performed) procedure. If you do not feel that Adept contributed to the event in either of these ways then score **N**.

	Relationship if any (score 1-5 as above)	Is this event serious as defined above? If <u>yes</u> please score A-D as above. If <u>no</u> please score N	Please indicate how Adept may have contributed (score M/L/P as above) If <u>no</u> please score N
<b>During surgery Event</b>			
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Post surgery Event</b>			
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Signature Responsible Surgeon

Contact point for queries: tel:

**Please fax any Adverse Event Reports as a matter of urgency to:**  
**Graeme Ladds, Head of International Pharmacovigilance, Shire Pharmaceuticals**  
**Tel: +44 (0)1256 894212 Fax: +44 (0) 1256 894715**  
**Alison Crowe, corvus. Tel: +44 (0) 1825 733057 Fax: +44 (0) 1825 732065**

**NOTE**

Please check all fields on form are completed and legible  
 Detach Patient Details Form  
 Copy Registry Form  
 Hold copy Registry Form with Patient Details Form for your own records

**Send original Registry Form to:**

**Prof. Sutton, ARIEL Co-ordination Group, c/o Alison Crowe, PO Box 155, UCKFIELD, TN22 4UA, UK**  
**Fax: +44 (0) 1825 732065 Tel: +44 (0) 1825 733057**

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## ARIEL GYNAECOLOGY REGISTRY FORM

To be completed in full and sent to:

Prof. Sutton, ARIEL Co-ordination Group, c/o Alison Crowe, PO Box 155, UCKFIELD, TN22 4UA, UK

Fax: +44 (0) 1825 732065

Tel: +44 (0) 1825 733057

Copy of form taken locally?  Yes  No    ARIEL Code:

Hospital:     Consulting Surgeon:

Operating Surgeon:     Grade:

Patient Date of Birth:     Date of Operation:

**PRESENTING SYMPTOMS**

Reason for admission  
Please detail:     Principle ICD9/10 code (if known):

Is there any history or evidence at surgery of Endometriosis?  Yes  No

If 'yes' please detail

Endometrioma <input type="checkbox"/> Deep Disease: <input type="checkbox"/> • Colon <input type="checkbox"/> • Rectovaginal <input type="checkbox"/> • Septum <input type="checkbox"/> • Uterosacral <input type="checkbox"/> Superficial Peritoneal Disease <input type="checkbox"/>	details <input style="width: 100%; height: 100px;" type="text"/>
--	---

**SURGERY UNDERTAKEN**

Elective     Laparotomy     Operation   
 Emergency     Laparoscopy     Indication:

Principle operation undertaken:     OPCS4 code (if known):

Other surgery (details):     OPCS4 code(s) (if known):

**ADHESIONS**    Were there any adhesions present at the time of surgery?  Yes  No

Details: (note extent, severity and sites)

Did you lyse these adhesions?  Yes  No

**SURGICAL HISTORY**

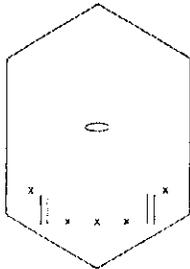
Previous surgery/surgeries:    Number  
 Laparotomies     date of most recent   
 Laparoscopies     date of most recent

Details (including history of adhesion related problems including Small Bowel Obstruction):

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**SURGICAL INCISION USED:**

**LAPAROSCOPY**



Circle trocar sites used and state size in mm

**LAPAROTOMY**

- Transverse suprapubic
- Mid line above umbilicus
- Mid line below umbilicus
- Paramedian

Other (detail)

**SURGICAL/USER EXPERIENCES**

**ADEPT irrigation during surgery and wash-out**

Batch No(s):

Total quantity used (ml):

- Method of irrigation:
- Laparoscopic Irrigation
  - Syringe
  - Other (detail)

ADEPT instillate at end of procedure: Batch No(s) As above:  or New:

**(NB 1 litre recommended)**

Total quantity used (ml):

Method of Instillation:

Other observations:

Total time of Surgery (from first incision to closure):  (min)

**ADEPT OBSERVATIONS**

Please score the following as **1-bad; 2-poor; 3-ok; 4-good; 5-excellent and note any observations**

Overall Satisfaction  Detail:

Viewing  Detail:

Handling  Detail:

Was there in any change in colour of residual fluid?  Yes  No Detail:

Other Observations:

**SURGERY CLOSURE**

Was there any leakage of peritoneal fluid/ADEPT at closure? (tick box)

- Less than normal
- As normal
- Moderate
- Excessive

How did you close the abdominal wall?

- Open Surgery**
- Mass Closure
- Layered Closure
- Laparoscopic Surgery**

Were port sites sutured (muscle/facial)?

- Yes  No

What method of wound closure did you use for skin?

Suture Type:

Glue Type:

Clips Type:

Other Observations:

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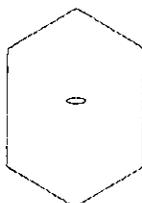
**SURGICAL OBSERVATIONS**

Did you place a drain at surgery?  Yes  No

If 'yes' was the volume of fluid draining greater than expected?  Yes  No

How much ADEPT was lost (please estimate)?  (ml) Over what period of time:  (min)

Please mark on the diagram where the drain was placed and where you think the tip may be positioned



Drain Position? (please mark)

Estimated position of tip of drain? (please mark)

Other observations:

Complications during surgery?  Yes  No If 'yes' details:

Postoperative complications?  Yes  No If 'yes' details:

Mortality?  Yes  No If 'yes' details:

Hospital Stay: from  to  Total days:  Time on I.C.U:  days

**CLINICAL OBSERVATIONS**

Abdominal discomfort (tick box)

Abdominal distension (tick box)

Less than expected

Less than expected

As expected

As expected

More than expected

More than expected

Of clinical concern

Of clinical concern

Any further comment/observations on ADEPT

Signature of Responsible Surgeon

Contact point for queries: tel:

**Sample of ARIEL General Surgery Registry Form**

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**'ARIEL'**  
**Adept Registry for clinical Evaluation**  
**GENERAL SURGERY REGISTRY**

**PATIENT DETAILS FORM**

Hospital:	<input type="text"/>	Consultant Surgeon:	<input type="text"/>
Operating Surgeon:	<input type="text"/>	Grade:	<input type="text"/>
Date of Operation:	<input type="text"/>	Patient Hospital No.:	<input type="text"/>
Patient initials:	<input type="text"/>	ARIEL Code:	<input type="text"/>
Date of birth:	<input type="text"/>	Weight:	<input type="text"/> kg    Height: <input type="text"/> m

**NOTE**

Allergies:  Yes     No

If 'yes'    Starch/Starch based Polymers-do not use ADEPT    Maltose/isomaltose-do not use ADEPT

Other (no contraindication for ADEPT) please detail

**NOTE IN COMPLETING THE ARIEL REGISTRY FORM**

Contributing surgeon to complete, detach and hold patient identifier information. This will enable you to verify queries and allow for subsequent audit of outcomes with your own patients.

Please ensure all fields on this Patient Details Form and the attached ARIEL Registry Form are completed before the Registry Form is submitted. If fields are not complete please detail why information is not available.

Please ensure writing is easily legible. Use of upper case may be helpful.

NB - Only complete forms fulfilling agreed criteria will be eligible for the Registry and analysed.

**NOTE**

Please detach this Patient Details Form

Please copy the attached Registry Form

Keep the original Registry Form with this Patient Details Form

Send the copied Registry Form to:

**Don Menzies, ARIEL Co-ordination Group, c/o Alison Crowe, PO Box 155, UCKFIELD, TN22 4UA, UK**

**Do not** send the Patient Detail Form

If you have any queries contact Alison Crowe +44 (0) 1825 733057 or Alistair Knight +44 (0) 208 891 1848

**POST DISCHARGE OBSERVATIONS**

Please record any observations/problems from post-discharge liaison

**ADVERSE EVENTS DURING AND POST SURGERY**

Shire have a statutory responsibility for reporting any Adverse Events. It is therefore imperative that if any occur that you complete the details on the form according to the scoring below and submit this form within 24 hours to allow for Shire to process and follow-up with you as needed.

Therefore:

1. Please list any adverse events that occurred during or post surgery and their relationship to ADEPT if any as per following score: **1-unrelated; 2-unlikely to be related; 3-possibly related; 4-probably related; 5-definitely related**
2. Please consider if these events were serious and if so please rate according to the following score:  
**A serious adverse event** is one which has led to: **A** - death; **B** - a life threatening illness or injury; **C** - permanent impairment of body function; **D** - a condition necessitating medical or surgical intervention to prevent impairment. If you do not feel the event was serious as defined then score as **N**.
3. Please also consider if the use of Adept may have contributed to the event according to the following:  
**M** – malfunction of Adept; **L** – labelling of Adept; **P** – deterioration in performance (extent of adhesion reduction or re-formation) of Adept, as assessed by comparing initial versus second-look (if performed) procedure. If you do not feel that Adept contributed to the event in either of these ways then score **N**.

	Relationship if any (score 1-5 as above)	Is this event serious as defined above? If <u>yes</u> please score A-D as above. If <u>no</u> please score N	Please indicate how Adept may have contributed (score M/L/P as above) If <u>no</u> please score N
<b>During surgery Event</b>			
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Post surgery Event</b>			
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Signature Responsible Surgeon

Contact point for queries:

tel:

**Please fax any Adverse Event Reports as a matter of urgency to:**

**Graeme Ladds, Head of International Pharmacovigilance, Shire Pharmaceuticals**

Tel: +44 (0) 1256 894212 Fax: +44 (0) 1256 894715

Alison Crowe, corvus. Tel: +44 (0) 1825 733057 Fax: +44 (0) 1825 732065

**NOTE**

Please check all fields on form are completed and legible

Detach Patient Details Form

Copy Registry Form

Hold copy Registry Form with Patient Details Form for your own records

**Send original Registry Form to:**

**Don Menzies, ARIEL Co-ordination Group, c/o Alison Crowe, PO Box 155, UCKFIELD, TN22 4UA, UK**

Fax: +44 (0) 1825 732065

Tel: +44 (0) 1825 733057

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## ARIEL GENERAL SURGERY REGISTRY FORM

To be completed in full and sent to:

Don Menzies, ARIEL Co-ordination Group, c/o Alison Crowe, PO Box 155, UCKFIELD, TN22 4UA, UK

Fax: +44 (0) 1825 732065

Tel: +44 (0) 1825 733057

Copy of form taken locally?  Yes  No

ARIEL Code:

Hospital:

Consulting Surgeon:

Operating Surgeon:

Grade:

Patient Date of Birth:

Date of Operation:

**PRESENTING SYMPTOMS**

Reason for admission  
Please detail:

Principle ICD9/10 code (if known):

**SURGERY UNDERTAKEN**

Elective

Laparotomy

Operation Indication:

Emergency

Laparoscopy

Principle operation undertaken:

OPCS4 code (if known):

Other surgery (details):

OPCS4 code(s) (if known):

**ADHESIONS**

Were there any adhesions present at the time of surgery?  Yes  No

Details:

(note extent, severity and sites)

Did you lyse these adhesions?

Yes

No

**SURGICAL HISTORY**

Number

Previous surgery/surgeries:

Laparotomies

date of most recent

Laparoscopies

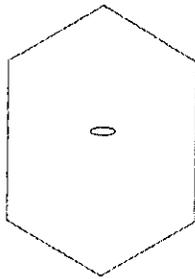
date of most recent

Details (including history of adhesion related problems and/or Small Bowel Obstruction):

**SURGICAL INCISION USED:**

LAPAROSCOPY

Mark trocar sites used and state size in mm



**LAPAROTOMY**

Transverse suprapubic

Mid line above umbilicus

Mid line below umbilicus

Paramedian

Other (detail)

**SURGICAL/USER EXPERIENCES**

**ADEPT irrigation during surgery and wash-out**

Total quantity used (ml):

Batch No(s):

Method of Irrigation: Laparoscopic Irrigation

Syringe

Other

Detail

ADEPT instillate at end of procedure: Batch No(s) As above:  or New:

(NB 1 litre recommended)

Total quantity used (ml):

Method of Instillation:

Other observations:

Total time of Surgery (from first incision to closure):  (min)

**ADEPT OBSERVATIONS**

Please score the following as

**1-bad; 2-poor; 3-ok; 4-good; 5-excellent and note any observations**

Overall Satisfaction

Viewing

Handling

Other observations

**SURGERY CLOSURE**

Was there any leakage of peritoneal fluid/ADEPT at closure? (tick box)

Less than normal

As normal

Moderate

Excessive

How did you close the abdominal wall?

**Open Surgery**

Mass Closure

Layered Closure

**Laparoscopic Surgery**

Were port sites sutured (muscle/facial)?

Yes  No

What method of wound closure did you use for skin?

Suture Type:

Glue Type:

Clips Type:

Other Observations:

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**SURGICAL OBSERVATIONS**

Did you place a drain at surgery?  Yes  No

If 'yes' what type of drain? Suction

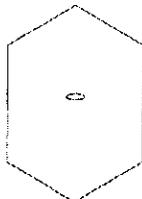
Non-suction tube drain

Other

Detail

What size of drain used?  mm

Please mark on the diagram where the drain was placed and where you think the tip may be positioned



Drain Position? (please mark)

Estimated position of tip of drain? (please mark)

Was the volume of fluid draining greater than expected?  Yes  No

How much ADEPT was lost (please estimate)?  (ml)

Over what period of time:  (min)

Other observations:

Complications during surgery?  Yes  No If 'yes' details:

Postoperative complications?  Yes  No If 'yes' details:

Mortality?  Yes  No If 'yes' details:

Hospital Stay: from  to  Total days:  Time on I.C.U:  days

**CLINICAL OBSERVATIONS**

Abdominal discomfort (tick box)

Abdominal distension (tick box)

Less than expected

Less than expected

As expected

As expected

More than expected

More than expected

Of clinical concern

Of clinical concern

Any further comment/observations on ADEPT

Signature of Responsible Surgeon

Contact point for queries: tel:

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**(v) Data Handling**

All participating surgeons were requested to submit their completed ARIEL forms for centralised data entry. In most instances forms were collected in batches through the local Shire Pharmaceutical affiliate and then sent to the UK for centralised processing.

An ACCESS database was used to capture data and this was formatted to follow the form structure for ease of data entry. Date handling was undertaken as follows; all returned forms were logged to allow tracking and checked for obvious queries and key field queries, including any adverse events. Data queries were raised and issued. Data entry systematically followed the information on the form. Most fields were tick boxes or numeric. Where there was text this was checked for legibility and where required translated with support from the local Shire operating company.

During data entry, a number of general data queries were identified. These included:

- Data fields incomplete
- The data fields illegible
- Data were lost to translation
- Data were lost to follow up
- Forms were inadequately completed

A standard handling and data entry/data query procedure was implemented to process all submitted forms.

**(vi) Data query management**

A total of 1454/4620 (31.5%) ARIEL forms were identified as having one or more data issues. Queries were raised and returned to surgeons for resolution. It is important to note that while the forms included a separate page for specific reporting of adverse events, any field that noted an event – eg intraoperative or postoperative complication – but which were not also recorded on the adverse event page, were returned to the surgeon requesting completion of the adverse event page – by way of soliciting and closely monitoring all events that occurred in patients in the Registry.

All forms with a query were returned for clarification and re-queried if on return they were not fully resolved.

In cases where translation of an adverse event was difficult, a Shire company physician made a judgement for the purpose of event categorisation. In the interests of safety, such evaluations were performed on a conservative basis.

In the case of inconsistent form completion (e.g. peri-operative or post-operative complication observed, but no adverse event section completed – despite query follow-up), a Shire physician made a decision on whether or not an event actually occurred, its seriousness and causality attribution. In most instances a second Shire physician also reviewed this. An independent surgical expert Safety Panel was also convened to provide independent scrutiny and opinion on event categorization and to advise on other safety analyses based on data within the ARIEL Registry.

### 6.2.3.2 Registry Adverse Event Reporting

The ARIEL Registry actively solicited events from contributing surgeons. While there was a specific page in the Registry Forms to allow for reporting of adverse events, there were free text fields in the forms to highlight any inter- or post-operative complications. If the latter fields had any record, which was not noted on the adverse event page, then a query was raised and the form returned for the contributing surgeon to complete the adverse event page. Shire Pharmacovigilance were also alerted in accordance with reporting of all coded adverse events. This ensured that all events were closely monitored.

Whereas Shire Pharmacovigilance coded all events as MedDRA in accordance with their Regulatory obligations, the ARIEL coordinators and the independent safety panel recommended ARIEL adverse events should be reported to the surgical community using clinical terms that were familiar to surgeons. The independent safety panel subsequently devised the higher and lower level terms which were used to report adverse events in the two ARIEL manuscripts. While the terms used were not dissimilar to MedDRA groupings, they were more clinical relevant and included a higher level term covering predicted irrigation and instillate events such as leakage of fluid/Adept from a port or wound site. This approach had the added benefit of providing for more specific and scientifically valid comparisons with the published background incidence of routine surgical events which are not MedDRA coded.

A full breakdown of these events, i.e. a frequency table, is provided in the SSED.

Surgery carries inherent post-operative complications such as pain, nausea, ileus and infection. Leaks may occur following any anastomotic procedure and fluid collections/oedema can occur when irrigant and instillate fluids are used during surgery.

In discussions with the independent safety panel it was felt that any comparison with background incidence of events should be based on all events reported in ARIEL and not those solely coded by surgeons as having a causal relationship to use of Adept since this would be a subjective assessment by the contributing surgeon.

For this reason in the manuscripts for publication (refer to Section 6 of the panel pack), the total incidence of events in ARIEL was presented and compared with background incidence rates identified from the published scientific literature. There was a larger volume of published evidence providing incidence of complications associated with general surgery than for gynaecological surgery. The independent safety panel were of the opinion that this reflected the view that gynaecological surgery is less prone to complications than general surgery.

In the general surgery manuscript the incidence of the predominant adverse events was compared with data from the published literature where there were data available as detailed overleaf and in the manuscript.

**Table 3 from General Surgery Manuscript - Incidence of adverse events that occurred in patients in the ARIEL general surgery registry ( $n = 1738$ ). The published adverse events rates are included for comparison where available**

Type of adverse event	Number of events (%)		Published adverse event rate (%)
	Laparotomy ( $n = 1469$ )	Laparoscopy ( $n = 269$ )	
Cardiac events	22 (1.5)	0 (0.0)	1–39 <sup>42–44</sup>
Fluid imbalance problems	11 (0.8)	1 (0.4)	2.3–4.5 <sup>45,46</sup>
Haematological events	20 (1.4)	3 (1.1)	–
Ileus	53 (3.6)	5 (1.9)	2.3–17.6 <sup>32,39</sup>
Pain	15 (1.0)	3 (1.1)	–
Predicted irrigation/instillation events	16 (1.1)	2 (0.7)	–
Respiratory events	56 (3.8)	3 (1.1)	–
Septic/infective events	61 (4.2)	9 (3.4)	2–40 <sup>40,47</sup>
Peritonitis	4 (0.3)	4 (1.5)	2.8–5.1 <sup>40</sup>
Surgical/technical events	43 (2.9)	6 (2.2)	–
Anastomotic wound-healing problems	27 (2.7)*	5 (7.6)*	1–39 <sup>31–36</sup>
Non-anastomotic wound-healing problems	56 (3.8)	2 (0.7)	0–6.5 <sup>47</sup>
Other	69 (4.7)	5 (1.9)	–

\*% of patients undergoing anastomotic procedures (laparotomy,  $n = 983$ ; laparoscopy,  $n = 66$ ).

### Background Incidences as published in the literature (extracted from ARIEL General Surgery manuscript)

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In the ARIEL Gynaecology manuscript as there was considerably less robust published background incidence rates these were not included in the table of adverse event incidences but overviewed in the Discussion of the paper. Reference: Sutton C, Minelli L, Garcia E, *et al.*, Use of icodextrin 4% solution in the reduction of adhesion formation after gynecological surgery (manuscript submitted to Journal of the American Association of Gynecological Laparoscopists, 17 December 2004), which is included in the Bibliography section.

For the purposes of this response a comparable table to that in the General Surgery manuscript is presented overleaf.

**Incidence of adverse events in the ARIEL gynaecological surgery registry ( $n = 2882$ ). The published adverse events rates are included for comparison where available.**

Adverse event	Number of events $n$ (%)		Published adverse event rate (%)
	Laparoscopy (2069 patients)	Laparotomy (813 patients) <sup>a</sup>	
Cardiac events	1 (0.1)	2 (0.3)	
Fluid imbalance problems	13 (0.6)	3 (0.4)	
Vulval edema	10 (0.5)	2 (0.3)	0.33 Laparoscopy <sup>1</sup>
Abdominal wall edema	2 (0.1)	0 (0.0)	
Hypovolaemic shock	0 (0.0)	1 (0.1)	
Ankle edema	1 (0.1)	0 (0.0)	
Hematological events	21 (1.0)	11 (1.4)	
Bleeding	16 (0.8)	7 (0.9)	
Haematoma	3 (0.1)	0 (0.0)	
Pulmonary embolism	1 (0.1)	2 (0.3)	
Thrombosis	0 (0.0)	2 (0.3)	
Decreased haemoglobin	1 (0.1)	0 (0.0)	
Ileus	3 (0.1)	8 (1.0)	0.1-0.5 Laparoscopy <sup>2</sup> 4.4-14.0 Laparotomy <sup>3,4</sup>
Pain	21 (1.0)	14 (1.7)	
<sup>b</sup> Predicted irrigation/instillation events	39 (1.9)	13 (1.6)	
Abdominal discomfort	3 (0.1)	20.3	
Abdominal distension	8 (0.4)	10.1	
Abdominal pelvic collections	7 (0.3)	20.3	
Port/wound leakage	21 (1.0)	8 1.0	
Respiratory events	0 (0.0)	3 (0.4)	
Septic/infective events	16 (0.8)	22 (2.7)	
Surgical/technical events	19 (0.9)	16 (2.0)	
Wound healing problems	3 (0.1)	10 (1.2)	
Other	20 (1.0)	11 (1.4)	

<sup>a</sup>Includes laparoscopies converted to laparotomies ( $n = 96$ ).

<sup>b</sup>Predicted irrigation/instillation events are inevitable events when using a fluid and are, therefore, not adverse events as such.

**Background Incidences as published in the literature**

- <sup>1</sup> Trout SW, Kemmann E. Vulvar edema as a complication of laparoscopic surgery. *J Am Assoc Gynecol Laparosc* 1996 4:81-83
- <sup>2</sup> Shen CC, Wu MP, Kung FT *et al*. Major complications associated with laparoscopic-assisted vaginal hysterectomy: ten-year experience. *J Am Assoc Gynecol Laparosc* 2003; 10:147-153
- <sup>3</sup> Steed HL, Capstick V, Flood C *et al*. A randomized controlled trial of early versus "traditional" postoperative oral intake after major abdominal gynecologic surgery. *Am J Obstet Gynecol* 2002; 186:861-865
- <sup>4</sup> MacMillan SL, Kammerer-Doak D, Rogers RG *et al*. Early feeding and the incidence of gastrointestinal symptoms after major gynaecologic surgery. *Obstet Gynecol* 2000; 96:604-608

As can be seen, the incidence rates of events reported in ARIEL were comparable with the expected rate of complications in surgery and no additional risk was apparently associated with Adept.



## 7. BIBLIOGRAPHY/REFERENCES

A reference listing is provided overleaf.

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All references highlighted in bold have been provided electronically.

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### **Literature Reports of 7.5% icodextrin and sterile peritonitis**

During the early part of 2002 there was an increase in reports of cloudy dialysate in peritoneal dialysis (PD) patients using Extraneal in Europe, and there have since been a number of publications in the literature reporting the experiences of individual nephrologists. These episodes of aseptic peritonitis have been attributed to contamination of specific batches of Extraneal with peptidoglycans.

Cloudy dialysate or abdominal pain in PD patients frequently indicates peritonitis associated with infection but there are other well documented non-infectious causes and episodes of culture-negative cloudy dialysate are referred to as aseptic or sterile peritonitis. Patients on PD have a risk for peritonitis, including aseptic peritonitis, in the order of 1 episode per patient year irrespective of their use of icodextrin.

In May 2002 Baxter initiated a voluntary recall of specific batches of Extraneal due to reports of sterile peritonitis and stated in a letter to nephrologists that some of these batches contained levels of peptidoglycan >10ng/ml. Elevated levels of peptidoglycan were observed in icodextrin from **one** of their icodextrin suppliers in Europe.

Investigations conducted by Baxter suggest that the source of these peptidoglycans was acidophilic thermophiles in the manufacturing plant.

Investigation of levels of peptidoglycan in 20 batches of icodextrin manufactured in the UK plant (owned at that time by ML Laboratories) demonstrated levels below the limit of detection for most batches and less than 1ng/ml for all batches tested at that time.

Investigations by Baxter have continued in both the UK plant and the alternative supplier's plant with a view to reducing the presence of acidophilic thermophiles (which has been achieved) and the levels of PGs in icodextrin.

Icodextrin manufactured at the UK plant is routinely monitored for PGs. This UK facility is the only source of icodextrin for Adept and for Extraneal in the United States.

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