P980053

SUMMARY OF SAFETY AND EFFECTIVENESS DATA:

DURASPHERE™ INJECTABLE BULKING AGENT

I. GENERAL INFORMATION

Device Generic Name:	Injectable Bulking Agent
Device Trade Name:	Durasphere™ (referred herein as Durasphere)
Applicant's Name and Address:	Advanced UroScience, Inc. 1290 Hammond Road St.Paul, Minnesota 55110
PMA Number:	P980053
Date of Panel Recommendation:	July 29, 1999
Date of Notice of Approval to the Applicant:	September 13, 1999

II. INDICATIONS FOR USE

Durasphere is indicated for use in the treatment of adult women with stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD).

III. DEVICE DESCRIPTION

Durasphere is a sterile, nonpyrogenic injectable bulking agent composed of pyrolytic carbon-coated zirconium oxide beads suspended in a water based carrier gel containing beta-glucan. The pyrolytic carbon-coated beads are designed to have a minimum dimension of 212 microns and a maximum dimension of 500 microns. The water-based carrier gel is approximately 97 percent water by volume and 3 percent beta-glucan.

Durasphere is injected sub-mucosally at the bladder neck in females. The injection of Durasphere creates increased tissue bulk and subsequent coaptation of the bladder neck. Over time collagen is deposited around the pyrolytic carbon-coated beads. The final bulking result derives from the combination of the pyrolytic-carbon coated beads and the body's own collagen.

8

IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

A. Contraindications

- Durasphere must not be used in patients with acute cystitis, urethritis or other acute genitourinary infection.

B. Warnings

- Do not inject Durasphere into blood vessels. Injection of Durasphere into blood vessels may cause vascular occlusion, platelet aggregation, infarction or embolic phenomena.

- Durasphere should not be used in patients with bladder neck or urethral strictures until such strictures have been corrected. Use of Durasphere on uncorrected strictures may cause occlusion.

- The safety and effectiveness of Durasphere treatment during pregnancy has not been established.

- The effect of Durasphere on subsequent pregnancy and delivery, and the impact of subsequent pregnancy on the effectiveness of Durasphere, is unknown. Therefore, the risks and benefits of the device in women of childbearing potential should be carefully assessed.

C. Precautions

- The treatment procedure and instrumentation associated with the injection of Durasphere carry an inherent, yet minimal risk of infection and/or bleeding, as do similar urologic procedures. The usual precautions associated with urologic procedures, specifically cystoscopy, should be followed.

- Durasphere is supplied steam sterilized in a sealed package and is intended for single use only. Carefully examine the unit to verify that neither the contents nor the sterile package has been damaged in shipment. **DO NOT USE** if damaged. Immediately return damaged product to Advanced UroScience.

- Do not re-sterilize. This may damage or distort contents. Unless the packaging is damaged, Durasphere will remain sterile until used.

- Do not expose to organic solvents, ionizing radiation or ultraviolet light. This may damage or distort contents.

- Rotate inventory so that product is used prior to the expiration date on package label.

- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.

- Long-term safety and effectiveness of Durasphere have not been established.

V. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The Durasphere clinical trial involved 300 Durasphere treatment injections in 178 female patients (mean time in study = 10.7 months, range = 0 to 24.9 months). Adverse events related to the use of Durasphere include: acute retention (duration ≤ 7 days) (16%), urinary urgency (13%), dysuria (12%), urinary tract infection (9%), hematuria (6%), non-acute urinary retention (duration > 7 days) (6%), outlet obstruction (slow prolonged stream) (4%), excreted bulking material (4%), GI problems (nausea, vomiting, diarrhea) (4%), genitourinary problems (infection, tenderness) (3%), urinary frequency (2%), and overbulking/abscess/cyst (2%).

Other adverse events were noted to occur infrequently (i.e., < 1%), have a duration of less than 24 hours, or were not categorized as device/treatment-related, and are summarized later in the Clinical Studies section.

Based on the literature, the following potential adverse events could occur but were not reported in the clinical trial: local tissue infarction and necrosis, erythema, embolic phenomena, and vascular occlusion.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative practices and procedures available for the treatment of female stress urinary incontinence include:

- external devices, such as pads/diapers, collecting devices, or occluding devices;
- internal urethral occluding devices;
- behavioral techniques and devices to assist in pelvic floor strengthening exercises, such as bladder training, prompted voiding, biofeedback, Kegel exercises (with or without vaginal cones), and electrical stimulation;
- pharmacological treatments, such as alpha-adrenergic agonists and estrogen supplements; and
- surgical treatments, such as suspension or sling procedures, urinary diversion procedures, artificial urinary sphincter prostheses, and other legally marketed injectable bulking agents.

VII. MARKETING HISTORY

Durasphere is marketed in the following countries: Austria, Germany, Italy, France, the United Kingdom, Singapore, and Australia. Additionally, Durasphere has been distributed outside the United States for clinical evaluation in New Zealand and in Costa Rica.

Durasphere has not been withdrawn from marketing for any reason related to the safety and effectiveness of the device.

VIII SUMMARY OF PRECLINICAL STUDIES

A. Bench Testing

Verification testing was performed on the various components of Durasphere injectable bulking agent to ensure conformance to specifications. The components that were tested include pyrolytic carbon-coated zirconium beads (e.g., 212-500 micron size range, 97.5% of beads (by weight) ≥ 250 microns), beta-glucan powder (e.g., < 2.5% protein), beta-glucan gel (e.g., 2.8% in water, viscosity > 10000 cps), and syringe plunger tips (protein <0.6 μg). All components evaluated were verified to meet the requirements of their specifications.

The following bench tests were conducted to evaluate the performance characteristics of the device:

- Wear Resistance: The beads were mixed in saline and repeatedly pumped through a closed fluid system (i.e., 500,000 cycles). Subsequent analysis verified that no additional particles were generated.
- Injection Force: Syringes with a new black stopper were tested and found to require less force to expel the Durasphere material than the syringes with the gray stopper that was earlier used in the clinical trial, indicating compliance with the expulsion force specifications.
- Syringe Leak Testing: Vacuum leak testing on empty Durasphere syringes indicated no leakage of the luer cap and/or the rubber seal of the plunger.
- Simulated Use Testing: Durasphere System simulated use testing simulated the actual opening of the syringe package and placing the syringe on to a sterile field. In this test, as expected, the lid peeled off easily, syringe fell out by itself and cap removal and needle connection/disconnection did not present any difficulty.
- Environmental and Transportation Testing: Environmental and transportation testing (according to ASTM D4169) verified that the conditions of transportation, temperature variation (-5^0 F to 125^0 F) and humidity changes (0% and 95%) did not affect the package tray integrity, box labels or Durasphere functionality in terms of wear resistance, flow characteristics and system simulated testing.

11

B. Sterilization and Shelf Life Testing

Steam sterilization of Durasphere syringes was validated to provide a sterility assurance level (SAL) of 10^{-6}. The heat sealing of blister packages was found to produce consistent seals with no deformation of the tray and lid. Accelerated aging testing on Durasphere syringes support a shelf life claim of 6 months.

C. Biocompatibility Testing

The Durasphere materials were evaluated for biocompatibility in accordance with the provisions of the GLP regulations, and FDA Blue Book Memorandum #G95-1. Testing included cytotoxicity, sensitization, systemic toxicity, hemolysis, muscle implantation (45 days), mutagenicity, and pyrogenicity. The results of these tests demonstrate that Durasphere materials are non-toxic, non-hemolytic, non-pyrogenic, and biocompatible.

Additional skin sensitization testing was conducted in a guinea pig model to evaluate skin reactivity to the beta-glucan material after intradermal injection. The results showed that repeated skin injections of glucan in various doses over a month's period of time did not elicit an allergic skin reaction. Biopsy of the skin test sites at different times revealed no histological evidence of immune reactivity compared to saline control sites.

D. Periurethral Implantation Studies in Dogs

Seven (7) day, 28-day, and 2-year GLP implant studies of Durasphere injectable bulking agent were conducted in dogs. The objectives of these studies were to determine the biocompatibility and migration potential of Durasphere implanted in the periurethral tissue of dogs. Organs associated with the immune system (lymph nodes, spleen, thymus, and gut-associated lymphoid tissues) were also examined in order to determine if the test article, especially beta-glucan, affected the immune system (7-day and 28-day studies). A total of 34 dogs were evaluated between the three studies. Follow-up evaluations were conducted at 2, 3 and 7 days (7-day study), 2, 3, 7, and 28 days (28-day study), and 3, 6, 12, and 24 months (2-year study).

It is important to note the following limitations of the 2-year study which had a significant impact upon the analysis of the results: (1) Durasphere was injected into the periurethral tissue via caudal abdominal incision (celiotomy) using a needle that is larger (16 gauge) than the one supplied clinically; these deviations from the actual clinical use of the device contributed to spilling and leakage of the material from the injection site. (2) The Durasphere used in this study was prepared prior to the addition of a bead washing step. The use of unwashed beads resulted in the introduction carbon soot and a finding of black granular particles at sites other than the injection site, making it difficult to determine whether there was migration of beads from the injection site.

The dog studies reported the following significant findings:

- There were no Durasphere related changes noted in the hematology, biochemistry, or urinalysis values throughout the 2-year time period.
- The tissue reaction to Durasphere was mild to moderate in the form of pyrogranulomatous, granulomatous and/ or subacute inflammation in the 7- and 28-day studies. At longer periods of implantation (3, 6, 12, and 24 months), the tissue reaction consisted of a mild chronic inflammatory reaction (including trace to mild gramulomas) that was fairly constant at all time periods with the findings at the 3-month time interval similar to those at all subsequent time periods. This reaction involved multifocal accumulations of macrophages with finely granular black pigment located inside and outside the cytoplasm at the implantation site, abdomen, mesentery, omentum and iliac lymph nodes. Considering that large particles in the 212-500 micron size range have not been reported to migrate to distant organs from periurethral injection sites, the finding of black granular particles in distant tissues/organs is considered to be the result of the use of unwashed beads and inappropriate injection technique.
- There were no signs of toxicity related to the periurethral administration of Durasphere.
- No differences were noted in the dogs receiving beta-glucan gel as compared to either saline or Durasphere injections other than a small number of vacuolated macrophages found in the 28-day study.
- No difference was detected in the number of reactive germinal centers in the organs examined (lymph nodes, spleen, thymus, gut-associated tissues) between the groups of dogs treated with saline, beta-glucan and Durasphere (7- and 28-day studies), suggesting that neither beta-glucan nor Durasphere caused generalized stimulation of the immune system.

It was concluded that the Durasphere material appears to be safe when injected into the periurethral tissues of dogs.

IX SUMMARY OF CLINICAL STUDIES

A. Study Objective

A clinical study was conducted under IDE G950085. The purpose of the clinical trial was to collect data for demonstrating the safety and effectiveness of Durasphere in the treatment of SUI due to ISD, and compare these data with those obtained for the control device (Contigen™ Bard® Collagen Implant).

B. Study Design

The study was a prospective, multi-center, double-blinded, randomized, controlled trial. Patients were randomized (1:1) to either Durasphere or the market-released control product (Contigen™ Bard® Collagen Implant). Patients and treatment evaluators were blinded to which device (Durasphere or control) the patient received. The patients were tested for skin sensitivity for Contigen™ collagen and beta-glucan, and only those who did not show a positive reaction in the test were subsequently treated with Durasphere or Contigen™. The patient's continence status was evaluated prior to treatment and at 1, 3,

6 and 12-month follow-up intervals following initial treatment. To evaluate whether the beads migrated to distant sites, KUB x-rays were taken at 12-month follow-up for Durasphere-treated patients.

The primary endpoint for determining the sample size was improvement of one incontinence grade (on Stamey Scale) at 12-month follow-up, compared to baseline grade. A sample size of 116 patients was calculated for each treatment arm, based on an equivalence trial using Blackwelder formula and the following assumptions:

α (one-sided type I error) = 0.05
β (type II error) = 0.20
Δ (difference between the effectiveness of test and control devices) = 0.15
P1 = P2 = 0.70 (expected success based on the primary endpoint)

Effectiveness Endpoints

The study had two primary effectiveness endpoints: (1) Improvement in continence grade from baseline to 12 months post-treatment; and (2) Improvement (decrease) in the amount of urine lost by patients who follow a prescribed protocol of activities, from baseline to 12 months post-treatment

The continence grades used for this study were defined by Stamey in 1979 and have been used increasingly over the past several years in different incontinence studies, including the Contigen™ clinical trials.

Grade 0:	Continent (dry).
Grade 1:	The patient will lose urine with sudden increases in abdominal pressure, but never in bed at night.
Grade 2:	The patient's incontinence worsens with lesser degrees of stress, such as walking, standing erect from a sitting position or sitting up in bed.
Grade 3:	The patient has total incontinence and urine is lost without any relation to physical activity or to position.

The urine loss was quantified through the use of pads, which were worn by the patients and then weighed at the completion of certain prescribed activities. A pad weight urine loss of ≤ 2 grams was considered to be the level of detectable change in the pad weight test.

The study had the following secondary effectiveness endpoints:

- The number of patients who had improvement in continence grade at follow-up intervals other than 1 year
- The number of patients who were totally cured (dry) at each follow-up interval
- The total number of treatments, including retreatments
- The volume of material injected
- Changes in Quality of Life

Safety Endpoints

The primary endpoint of safety was evaluated through an analysis of morbidity and complication rates associated with the use of Durasphere, and the evaluation of those risks. Symptoms and complications were recorded on all patients. The investigators were instructed to report any symptom or adverse experience, and to rate each experience for intensity, duration, possible cause, and outcome. All reports of adverse experiences were reviewed and classified in terms of nature and severity of the event as well as the relationship of event to the device or to the treatment procedure.

C. Study Protocol

Patient Selection

The patient population in the clinical trial consisted of both men and women who were diagnosed with SUI due to ISD.

The inclusion criteria for study enrollment included:

- Age ≥ 21 years
- Failure of prior, non-invasive treatments
- Duration of incontinence > 12 months
- Post-void residual volume < 100 ml

The primary exclusion criteria were:

- Types of incontinence other than SUI due to ISD
- Allergy to bovine collagen products
- Malignancy
- Pelvic radiotherapy
- Uncontrolled bladder instability
- Absence of viable mucosal lining at the injection site
- Positive urine culture
- Active gross hematuria
- Neurogenic bladder
- Previous implantation of an artificial urinary sphincter
- Medications affecting bladder function
- Acute cystitis or urethritis
- Pregnancy anytime in previous 12 months (or planned pregnancy in next 24 months)
- Chronic disease or diminished mental capacity that would interfere with the patient's ability to comply with the protocol

Patients willing to participate in the study and who signed a consent form underwent a basic evaluation of their urinary incontinence. This evaluation included a history, physical examination, urodynamic test, pad weight test, blood work, urinalysis, and both a control and Durasphere skin test. Only those individuals satisfying the inclusion and exclusion criteria were allowed to participate.

Treatment Procedures

Patients who did not demonstrate a response to the skin test within the 28-day observation period and who were otherwise eligible for treatment were treated with either Durasphere or the control. A treatment was defined as one or more injections of Durasphere or the control on a specific date, as this bulking material could be injected at several sites in the periurethral tissue during any given treatment.

Durasphere was injected transurethrally under direct visualization, through a cystoscope or endoscope via the Advanced UroScience Injection Needle into the mucosal lining of the bladder neck. The syringe of Durasphere was attached to the injection needle. Patients randomized to the control group had the bulking agent injected according to the control material Directions for Use.

It is recommended that patients be kept in the setting or clinic where they receive their Durasphere injection until they are able to void on their own volition. In the event the patient experiences urinary retention, it can be managed by catheterization in the immediate post-injection phase and with clean intermittent catheterization should it persist.

The total number of retreatments a patient could ultimately receive was limited to four. Retreatment was to occur when the patient had not improved or when the investigator believed that another treatment would be beneficial to the patient.

Study Variables

Upon enrollment into the study, baseline patient and medical history data relevant to the diagnosis of SUI were collected. At baseline and follow-up visits (1, 3, 6, and 12 months), data were also collected on the results of laboratory blood and urine testing, abdominal leak point pressure testing, pad weight tests, voiding diaries, and Incontinence Quality of Life (IQOL) questionnaire.

In addition to the assessment of changes in continence grade at scheduled follow-ups, data were recorded on any procedure- or urology-related symptoms and adverse effects.

D. Description of Study Population

A total of 578 female patients and 31 male patients were tested for skin reaction. Of the 578 women tested for skin reaction, 57 voluntarily withdrew (includes 8 who had tested positive initially to Durasphere and withdrew), 155 did not meet inclusion/exclusion criteria (124 failed physical exam or urodynamics and 31 had a positive skin test to Contigen™) and 11 tested positive initially to Durasphere but not on retesting. These 11 patients were treated with Durasphere but were not included in the treatment information presented in the PMA. These withdrawals/exclusions left a total of 355 patients eligible for treatment, 178 of whom were treated with Durasphere and 177 of whom were treated with control. These patients were enrolled in the study between July 10, 1996, and December 1, 1998, and all follow-up data received by May 21, 1999, are reported in the PMA. Of the female patients treated with either Durasphere or control,

12-month follow-up data were available on 115 and 120, respectively. The withdrawal/lost-to-follow-up rates associated with these 12-month follow-up cohorts are 11.5% and 7% for the Durasphere and control arms, respectively.

Of the 31 males patients tested for skin reaction, a total of 22 were randomized into the study (10 Durasphere and 12 control). Since the number of male patients is too small to statistically analyze, conclusions could not be drawn regarding the safety and effectiveness of the use of Durasphere in men. Therefore, the remainder of this summary refers only to female subjects.

Nine U.S. sites and one foreign site (San Jose, Costa Rica) participated in the trial. The Costa Rican site treated a total of 62 female patients (31 patients each receiving Durasphere and control).

Patient Baseline Characteristics

Table 1 displays the baseline characteristics of the patients injected with Durasphere and the control product. There was no significant difference between Durasphere and control patients for any of the baseline variables.

Table 1. Summary of Patient Baseline Characteristics

Characteristic	Durasphere (n = 178)	Control (n = 177)	p-Value
Mean Age (yr.)	57.7	57.0	0.598
Race			0.900
Caucasian	80.3%	79.1%	
Hispanic	18.0%	19.8%	
African-American	1.1%	1.1%	
Other	0.6%	0	
Etiology			
Childbirth	71.3%	68.4%	0.564
Prior Surgery	19.7%	15.3%	0.328
Trauma	4.5%	2.8%	0.574
Other	6.7%	7.9%	0.690
Duration of Incontinence (yr.)	10.3	10.1	0.887
Baseline Symptoms			
Nocturia	61.2%	56.5%	0.389
Frequency	48.9%	48.0%	0.916
Increased Leakage	43.3%	46.9%	0.523
Urgency	35.4%	31.6%	0.500
Suprapubic Pain	10.7%	9.6%	0.861
Dysuria	7.3%	3.4%	0.156
Poor Stream	6.2%	6.8%	0.833
Hesitancy	5.6%	5.1%	1.000
Loss of Urine with Other Symptoms	5.1%	4.5%	1.000
Perineal Pain	4.5%	4.5%	1.000
Hematuria	4.5%	2.8%	0.574
Straining	2.8%	2.8%	1.000
Baseline Urodynamic Parameters			
Mean PVR (ml)	15.76	12.81	0.233
Mean aLLP (cm H_2O)	51.81	50.42	0.514
Mean Baseline Continence Grade Score	1.87	1.91	0.476
Baseline Management of Incontinence			
Patients Using Pads or Briefs	96.1%	95.5%	0.799
Mean # of Pads/Briefs Used per Day	2.6	2.7	0.795
Mean Pad Weight (gm)	46.4	41.5	0.384
Baseline Mean # of Incontinence Episodes per Week	21.6	23.0	0.596

It is important to note that 19% (34/178) of the patients had a baseline incontinence grade of 1, 75% (133/178) had a baseline grade of 2; and only 6% (11/178) had a baseline incontinence grade of 3.

Skin Test Results

A total of 578 patients were tested for skin sensitivity to Durasphere and Contigen™ at the U.S. sites (n=485) and in Costa Rica (n=93). In this test, 19/93 patients (20.4%) in Costa Rica were determined to have a positive reaction, using conservative criteria

(probably including an inflammatory reaction) for evaluating the skin reaction. On reevaluation, using a different but valid protocol for the skin test and evaluation of the result by a qualified allergist/immunologist, only 1/93 Costa Rican patients was confirmed to have a positive reaction to the Durasphere skin test (not life-threatening in nature). Excluding the Costa Rican patients, 17/485 (3.5%) U.S. patients had a positive reaction to the control material.

Treatment Information

Table 2 summarizes the treatment-related data for the 178 subjects in the Durasphere arm. As described below, 43% (49/115) of the patients who were followed for 12 months received a single treatment, 40% (46/115) received two treatments and 13% (15/115) received three treatments. Since the follow-up was counted from the initial treatment, only those who received a single treatment (i.e., 43%) had no treatment injections during the 12-month follow-up period.

Table 2. Treatment Information

Mean number of treatments per patient during study	1.7
Patients receiving a single treatment and followed for 12 months Patients receiving two treatments and followed for 12 months Patients receiving three treatments and followed for 12 months Patients receiving > three treatments and followed for 12 months	43% (49/115) 40% (46/115) 13% (15/115) 4% (5/115)
Mean time between treatments	5.3 months
Mean initial volume injected per patient	4.8 ml
Mean total volume injected per patient	7.6 ml

E. Effectiveness Results

Primary Effectiveness Endpoints

One primary endpoint is the percentage of patients that improved by ≥ 1 continence grade at 12 months. As shown in Table 3, 66.1% (76/115) of Durasphere patients and 65.8% (79/120) of control patients demonstrated an improvement of ≥ 1 continence grade at 12 months. No significant difference was observed between Durasphere and the control group (p=1.00).

Table 3. Improvement of ≥ 1 Continence Grade at 12 Months

Follow-up Visit	Durasphere		Control		p-Value[1]
	n/Total	%	n/Total	%	
12 Month	**76/115**	**66.1%**	**79/120**	**65.8%**	**1.000**
[1]Two-sided Fisher's Exact Test					

Likewise, the dryness (Grade 0) rates at 12 months were also identical between the Durasphere and control groups: 31.3% (36/115) and 30.8% (37/120), respectively.

As summarized in Table 4, the other primary effectiveness endpoint, change in pad weight urine loss from baseline to 12 months, was also similar between Durasphere and control (27.9 gm reduction for Durasphere, and 26.4 gm reduction for control). For Durasphere, this reduction in pad weight urine loss reflected a mean reduction of 59% (27.9 gm average loss at 12-month follow-up/47.2 gm average loss at baseline).

Table 4. Improvement in Pad Weight from Baseline to 12 Months

Follow-up Visit	Durasphere		Control		p-Value[1]
	n	Mean Change (SD)	N	Mean Change (SD)	
12 Month	**113**	**27.9 (43.6)**	**117**	**26.4 (63.7)**	**0.835**
[1]Two-sided Student's *t*-test					

Table 5 summarizes the results of additional analyses of the primary effectiveness endpoints among Durasphere-treated patients.

Table 5. Effectiveness Results

Patients receiving a single injection and dry (grade = 0) at 12 months Patients receiving a single injection and improved (≥ 1 grade) at 12 months	47% (23/49) 84% (41/49)
Patients receiving ≥ 2 injections and dry (grade = 0) at 12 months Patients receiving ≥ 2 injections and improved (≥ 1 grade) at 12 months	20% (13/66) 53% (35/66)
Patients with a baseline grade > 1[†] and dry (grade = 0) at 12 months Patients with a baseline grade > 1[†] and improved (≥ 1 grade) at 12 months	31% (29/94) 73% (69/94)
Patients dry (grade = 0) at one or more follow-up examination(s) Patients improved (≥ 1 grade) at one or more follow-up examination(s)	58% (101/175) 90% (158/175)
Mean improvement (decrease) in pad weight at 12 months	27.9 gm (59%)
Mean improvement (decrease) in # incontinence episodes/week at 12 months	20.8 (51%)

[†] A total of 94 patients with baseline grade > 1 were followed for 12 months; 89 had baseline grade 2 and 5 had grade 3.

There was no significant difference in the effectiveness of Durasphere compared to the control group. Additionally, although few patients with severe incontinence (i.e., baseline grade 3) were treated with Durasphere, the effectiveness of the device is these patients was similar to that observed in patients with baseline grades 1 and 2. For example, at 12-month follow-up 73% (65/89) of baseline grade 2 patients were improved as compared to 80% (4/5) of baseline grade 3 patients. Likewise, 30.3% of baseline grade 2 patients were dry, as compared to 20% (1/5) baseline grade 3 patients.

20

Secondary Effectiveness Endpoints

Continence Grade

- The mean continence grade for Durasphere patients was significantly improved (48% reduction) from 1.86 at baseline to 0.97 at 12 months ($p < 0.001$).
- The mean continence grade was significantly improved (reduced) from baseline to all follow-up time periods for Durasphere patients ($p < 0.001$, all intervals).
- No significant difference in mean change in continence grade was observed between Durasphere and the control group at any of the follow-up visits.
- No significant difference was observed between the proportion of Durasphere and control group patients who demonstrated improvement by ≥ 1 continence grade at any of the follow-up intervals.
- No significant difference was observed between the proportion of Durasphere and control group patients who achieved a continence grade of 0 ("dry") at any of the follow-up intervals.
- No significant difference was observed in the actuarial curves (probability of maintaining a one grade improvement over time) between Durasphere and the control group.

Pad Weight

- The mean pad weight was significantly improved (reduced) from baseline to follow-up at all time periods for Durasphere patients ($p < 0.001$ at 1, 3, 6, 12 months, $p=0.003$ at 18 months).
- No significant differences in mean change in pad weight from baseline to follow-up was observed between Durasphere and control group at any of the follow-up visits.

Incontinence Episodes

- The mean number of episodes per week for Durasphere patients was significantly improved from 20.8 at baseline to 10.2 at 12 months ($p < 0.001$).
- The mean number of episodes per week was significantly improved (reduced) from baseline to follow-up at 1, 3, 6, 12 months for Durasphere patients ($p < 0.001$).
- No significant difference in mean change in number of incontinence episodes from baseline to follow-up was observed between Durasphere and control group at any of the follow-up visits.

Quality of Life

- The mean score for Durasphere patients was significantly improved from 55.5 at baseline to 73.7 at 12 months ($p < 0.001$).
- The mean QOL score was significantly improved (increased) from baseline to follow-up at all time periods for Durasphere patients ($p < 0.001$).
- No significant difference in mean change in QOL scores from baseline to follow-up was observed between the two groups at any of the follow-up visits.

Volume Injected and Number of Treatments

- Durasphere patients had significantly less material injected at the initial injection (4.83 ml for Durasphere, 6.23 ml for control), as well as total material injected during the study (7.55 ml for Durasphere, 9.58 ml for control) ($p < 0.001$). However, this difference does not appear to be clinically meaningful.
- There was no significant difference in the number of treatments between the two groups. The mean number of injections was 1.69 for Durasphere and 1.55 for the control group patients.

F. Safety Results

Adverse events

The primary endpoint of safety was analysis of morbidity and complication rates associated with the use of Durasphere, and the evaluation of those risks. All of the adverse events reported during the clinical study (i.e., treatment related and non-treatment related) for Durasphere that lasted for > 24 hours are shown in Table 6.

Table 6. All Adverse Events (treatment related and non-treatment related)

	# Pts	% Pts	# Events
Urinary tract infection	53	29.8%	64
Urinary urgency	44	24.7%	48
Dysuria	32	18.0%	38
Acute retention (duration ≤ 7 days)	30	16.9%	33
Respiratory (infection)	19	10.7%	21
GI (nausea, vomiting, diarrhea, rectal bleeding, inflammation)	19	10.7%	20
Non-acute retention (duration > 7 days)	19	10.7%	19
Genitourinary (infection, tenderness, urethral prolapse, uterine bleeding, detrusor instability)	17	9.6%	21
Hematuria	12	6.7%	12
Musculoskeletal (back/leg problems, arthritic changes)	10	5.6%	11
Urinary frequency	10	5.6%	10
Outlet obstruction (slow prolonged stream)	8	4.5%	8
Cardiac (angina, MI, hypertension, edema, CAD)	7	3.9%	8
Excreted bulking material	7	3.9%	7
Pain (pelvic, flank, back, ear)	6	3.4%	6
Surgery (hysterectomy, cataract, foot, chole)	6	3.4%	6
Infection (dental, viral, groin)	5	2.8%	6
Accident (fractures/fall)	5	2.8%	5
Overbulking/abscess/cyst	4	2.2%	4
Abnormal lab values	3	1.7%	4
Peripheral vascular (edema, phlebitis)	3	1.7%	3
Dermatology (rash)	3	1.7%	3
Allergic reaction to antibiotic	3	1.7%	3
Fever	3	1.7%	3
Worsening of incontinence (onset of urge)	3	1.7%	3
Neurological (headache, dizziness)	2	1.1%	2
Renal symptom (failure)	1	0.6%	1
Psychological (depression)	1	0.6%	1

There were no deaths among the patients injected with Durasphere during the course of this trial. There is no statistically significant difference in 29 categories between the rates reported for Durasphere and control. However, there was a significantly higher incidence of urgency and acute retention (duration ≤ 7 days) for Durasphere (24.7%, 16.9%) than for control patients (11.9%, 3.4%), ($p = 0.002$, $p < 0.001$, respectively). The granulomatous inflammation and/or subacute inflammation observed in the 7-day dog study may offer a reasonable explanation for the higher incidence of urgency and acute retention observed in the Durasphere patients. Other conclusions from comparison of the adverse events among the Durasphere and control arms are as follows:

- The resolution of urgency events was significantly better (higher) for Durasphere (89.6%) than for the control group (65.2%), ($p = 0.021$).
- Approximately forty-nine percent (48.6%) of all adverse events were resolved within 2 weeks of injection and 91.4% of all the adverse events were resolved as of the database cutoff for Durasphere, compared to the resolution of 86.7% at time of database cutoff for the control group.
- The overall mean duration for all adverse events was significantly better (lower) for Durasphere (70.0 days) compared to the control group (82.8 days) ($p = 0.032$).
- There was no significant difference seen in the distribution of severity of events between Durasphere patients and the control patients.

Forty-four percent (44.0%) of all the adverse events were treatment related and are shown in Table 7 below. Treatment related events are those events that the investigator deemed device related or procedure related. In general, the onset of treatment related events was closer to the treatment date compared non-treatment related events. For example, the mean number of days between treatment and onset of UTI, urgency, dysuria and non-acute retention was 11 days for treatment related events compared to 126 days for non-treatment related events.

Table 7. Treatment Related Adverse Events

	# Pts	% Pts	# Events
Acute retention (duration ≤ 7 days)	29	16%	32
Dysuria	22	12%	26
Urinary urgency	23	13%	25
Urinary tract infection	16	9%	18
Hematuria	11	6%	11
Non-acute retention (duration > 7 days)	10	6%	10
Outlet obstruction (slow prolonged stream)	8	4%	8
Excreted bulking material	7	4%	7
GI (nausea, vomiting, diarrhea)	7	4%	7
Genitourinary (infection, tenderness)	5	3%	5
Urinary frequency	4	2%	4
Overbulking/abscess/cyst	3	2%	3
Infection	1	< 1%	2
Worsening of incontinence (onset of urge)	1	< 1%	1
Neurological (headache)	1	< 1%	1
Pelvic pain	1	< 1%	1
Allergic reaction to antibiotic	1	< 1%	1
Fever	1	< 1%	1

In addition to the adverse events summarized above (duration > 24 hours), 107 patients experienced transient symptoms lasting < 24 hours, which were defined as transient. The following transient symptoms were observed during the clinical trial: hematuria (58 patients, 33%), urinary retention (30 patients, 16%), urgency (26 patients, 14%), dysuria (22 patients, 12%), frequency (7 patients, 4%), excreted bulking material (7 patients, 4%), gastrointestinal symptoms (6 patients, 3%), genitourinary symptoms (2 patients, 1%), headache (1 patient, <1%), worsening of incontinence (1 patient, <1%), outlet obstruction (1 patient, <1%), pain (1 patient, <1%), and fever (1 patient, <1%).

12 Month KUB X-rays

Post-treatment KUB x-rays taken at 12 months on 100 patients and at 18 and 24 months on a smaller number of patients showed no evidence of migration of the pyrolytic carbon-coated zirconium oxide beads.

X. CONCLUSIONS

- Durasphere injection is safe to use for treating the symptoms of SUI due to ISD. No safety issues arose with respect to the injected material or the delivery system when used according to its instructions for use. Most of the safety data are limited to 1 year and long-term safety of Durasphere in patients is unknown (see Precautions in Labeling).
- Durasphere injection has been effective in reducing SUI, as measured by improvement in continence grades, pad weight tests, incontinence episodes, and quality of life instruments.
- The effectiveness of Durasphere was found not to be significantly different than that of the commercially available Contigen™ control device in a prospective, controlled, randomized clinical trial, with significantly less injected material required on average to obtain comparable clinical benefit.
- Skin reactivity testing in human subjects has shown that a positive reaction to Durasphere is rare (1/578). This finding in conjunction with the absence of an allergic or immune response in animals indicates that pretreatment skin test for Durasphere is not necessary.
- Durasphere implantation in the periurethral tissue of dogs did not elicit a toxic response. The chronic low level (mild) inflammatory/granulomatous response observed in the dog studies is considered a normal tissue response to a foreign body. This chronic response remained essentially constant during the Durasphere implantation period of 3 to 24 months.

XI. PANEL RECOMMENDATIONS

The Gastroenterology-Urology Devices Panel met on July 29, 1999, to consider the safety and effectiveness of Advanced UroScience's Durasphere. The Panel recommended that the Center for Devices and Radiological Health (CDRH) approve the

PMA for Durasphere, subject to the following conditions: (1) revised labeling indicating the device for use in adult (over 21 years of age) male and female patients, including a statement that there are minimal data on men, children and women of reproductive age; (2) post-approval study designed to collect more data on the device effectiveness in Grade 3 patients and men, and safety in children and women of reproductive age; and (3) restriction of device use to physicians trained in therapeutic endoscopy.

XII CDRH DECISION

CDRH agreed with the Panel's recommendation that the device is approvable, however CDRH disagreed with the Panel's recommendation that Durasphere be indicated for use in men because (1) few men were treated with Durasphere and (2) of those treated and followed for 12 months, none showed improvement. This finding supports the sponsor's statement that, based on the anatomical and etiological differences, the treatment results are gender-specific. Since CDRH decided that Durasphere should be indicated only for adult women, the revised labeling does not have to address the lack of data on men and the post-approval study is not required to include men. CDRH agreed with the other recommendations of the Panel and conveyed its decision about the labeling requirements and the post-approval study to Advanced UroScience over the telephone and by fax. The firm responded by submitting revised labeling and post-approval study protocol. The post-approval study is a 5-year study after the first treatment and is intended to evaluate the durability or maintenance of the improvement observed at the 12-month follow-up. Only patients who showed one grade improvement in their incontinence are followed and a minimum of 56 patients are expected to have the 5-year follow-up.

FDA inspections of the manufacturing and sterilization facilities determined that the applicant was in compliance with the Quality Systems regulation.

CDRH issued an approval order for the application on September 13, 1999.

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See labeling

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

Post-approval Requirements and Restrictions: See approval order.