Solesta® Injectable Gel

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

INDICATION FOR USE

Solesta® is indicated for the treatment of fecal incontinence in patients 18 years and older who have failed conservative therapy (e.g., diet, fiber therapy, anti-motility medications).

DEVICE DESCRIPTION

Solesta consists of dextranomer microspheres, 50 mg/mL, and stabilized sodium hyaluronate, 15 mg/mL, in phosphate-buffered 0.9% sodium chloride solution.

Solesta is a sterile, viscous, biocompatible bulking agent contained in a disposable 1 mL assembled glass syringe with a standard Luer-lock fitting. The syringe is equipped with a plunger stopper, a plunger rod and a finger grip. The labeled syringe is packed in a pouch and terminally sterilized by moist heat. The final product consists of a carton containing four pouches with syringes, four sterile needles (SteriJect®, 21G x 4 ¾ inches, 0.80 x 120 mm), patient record labels and a package insert. The product is for single use.

Both the dextranomer and sodium hyaluronate are made up of biosynthesized polysaccharides of non-animal origin. The dextranomer component consists of microspheres of dextran chains cross-linked into a three-dimensional network. The stabilized sodium hyaluronate accounts for the viscous properties of Solesta and acts as a carrier that facilitates the injection of the dextranomer microspheres.

Solesta is injected in the deep submucosal layer in the proximal part of the high pressure zone of the anal canal about 5 mm above the dentate line. A total of 4 submucosal injections of 1 mL Solesta are administered at each treatment session.

CONTRAINDICATIONS

Solesta is contraindicated in patients with the following conditions:

- Active inflammatory bowel disease
- Immunodeficiency disorders or ongoing immunosuppressive therapy
- Previous radiation treatment to the pelvic area
- Significant mucosal or full thickness rectal prolapse
- Active anorectal conditions including: abscess, fissures, sepsis, bleeding, proctitis, or other infections
- Anorectal atresia, tumors, stenosis or malformation
- Rectocele
- Rectal varices
- Presence of existing implant (other than Solesta) in anorectal region
- Allergy to hyaluronic acid based products

WARNINGS

- Do not inject Solesta intravascularly. Injection of Solesta into blood vessels may cause vascular occlusion.
- Injection in the midline of the anterior wall of the rectum should be avoided in men with enlarged prostate.

PRECAUTIONS

General precautions

- Solesta should only be administered by physicians experienced in performing anorectal procedures and who have successfully completed a comprehensive training and certification program in the Solesta injection procedure.
- The safety and effectiveness of Solesta have not been investigated in patients with complete external sphincter disruption or significant chronic anorectal pain.
- The safety and effectiveness of Solesta have not been investigated in patients with previous procedures involving the anorectal region: rectal anastomosis <12 cm from anal verge, anorectal surgery within previous 12 months, hemorrhoid treatment with rubber band within 3 months, anorectal implants and previous injection therapy, Stapled Transanal Rectal Resection (STARR) or stapled hemorrhoidectomy.
- The safety and effectiveness of Solesta have not been studied in patients under the age of 18 years.
- The safety and effectiveness of Solesta have not been studied in pregnant or breastfeeding women.
- The durability of Solesta has not been studied past 36 months.
- The safety and effectiveness of Solesta have been studied in patients who received one or two treatments. In the Pivotal study, the majority of patients received two treatments, four weeks apart.

Patient related precautions

- Patients with bleeding diathesis or patients using anticoagulant or antiplatelet agents, as with any injections, may experience increased bleeding at injection sites.
- Patients should be counseled that a repeated Solesta injection procedure may be required to achieve a satisfactory level of improvement in incontinence.

Procedure related precautions

- Adequate bowel preparation of the rectum using enema is required prior to injection. The enema should be given immediately prior to the procedure to ensure evacuation of the anorectum. It is recommended that additional cleansing of the injection area with an antiseptic be performed prior to injection. Use of prophylactic antibiotics is recommended.
- Solesta should be injected slowly to avoid undue stress on the Luer-lock connection which could cause leakage of the gel.
- After injection of Solesta, hold the needle at the injection site for an additional 15-30 seconds to minimize leakage of Solesta.
- Injections too close to the dentate line or too deep in the tissue might cause excessive pain.
- Injection should be stopped if excessive bleeding or pain occurs.
- One sterile needle should be used per syringe and injection.

Device related precautions

- The use of needles other than those supplied may impede injection of Solesta due to the properties of the gel and may cause device malfunction.
- Solesta is supplied ready to use in a prefilled syringe with a Luer-lock fitting. Carefully examine the unit to verify that neither the contents nor the package has been damaged in shipment. Do not use if damaged.
- Solesta is supplied sterile and is intended for single use only. Do not re-sterilize, as this may damage or alter the product.
- In the event of accidental contamination of a needle, discard the needle.
- Never mix Solesta with other products.
- Solesta is to be stored at up to 25°C (77°F), and used prior to the expiration date printed on the label. Do not expose Solesta to either sunlight or freezing, as this may damage or alter the product.
- Care should be taken when handling the glass syringes and disposing of broken glass to avoid laceration or other injury.
- After use, syringes and needles should be handled as potential biohazards. Disposal should be in accordance with accepted medical practice and applicable local, state and federal requirements.

ADVERSE EVENTS

The adverse event profile of Solesta was investigated up to 36 months post injection. Adverse events considered possibly or probably related to Solesta treatment include the following events that were experienced by at least 2 patients in the Pivotal study (Table 5 in the Clinical Studies section): proctalgia, injection site hemorrhage, rectal hemorrhage, pyrexia, diarrhea, injection site pain, anorectal discomfort, anal hemorrhage, rectal discharge, proctitis, anal prolapse, constipation, anal pruritus, lower abdominal pain, defecation urgency, painful defecation, rectal obstruction, chills, injection site nodule, pain, rectal abscess, rectovaginal septum abscess, dyspareunia, and alopecia. Adverse events considered possibly or probably related to Solesta treatment and reported for only 1 patient each are listed in the footnote to Table 5.

The observed adverse events are discussed in the Clinical Studies section below.

CLINICAL STUDIES

Introduction

Clinical data supporting the safety and effectiveness of Solesta are available from three clinical studies: 1) a pivotal, prospective, multicenter, randomized, sham-controlled double-blind study of 206 patients conducted under an Investigational Device Exemption (IDE; Pivotal study), 2) a prospective, multicenter, open-label study of 115 patients conducted outside the United States (Open-Label study), and 3) a single center study of 34 patients conducted at one site in Sweden (Proof-of-Concept study). The Pivotal study also included a cross-over option for patients initially randomized to Sham. The majority of patients (over 84%) in all three studies were female.

Table 1 provides an overview of the design of the three studies.

Table 1: Comparison of the three clinical studies supporting safety and effectiveness of Solesta

	Pivotal study	Open-Label study	Proof-of-Concept study
Study Design	Randomized double-blind comparative study of Solesta versus Sham in 2:1 ratio	Open study	Open study
Primary Efficacy Endpoints	Effectiveness: (1) Superiority in proportion Responder$_{50}$ compared with Sham at 6 months (2) Durability of response based on proportion responders at 12 months Durability of response was also evaluated up to 36 months following last injection	Effectiveness: Proportion Responder$_{50}$ at 12 months Durability of response was also evaluated up to 24 months following last injection	Effectiveness: Proportion Responder$_{50}$ at 12 and 24 months
Secondary Efficacy Variables	Fecal Incontinence Quality of Life (FIQL) Scale	FIQL	SF-36 European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30
	Cleveland Clinic Florida Incontinence Score (CCFIS)	CCFIS	Miller Score
	Fecal Incontinence (FI) free days	FI free days	FI free days
	Fecal Incontinence (FI) episodes, controlled bowel emptying, medications	FI episodes, controlled bowel emptying, medications	FI episodes, global evaluation by patient, patient subjective judgment of treatment effect
Investigational Centers	8 centers in US and 5 centers in Europe	14 centers in Europe and 1 center in Canada	1 center in Sweden
Sample Size	136 patients randomized to Solesta, and 70 patients randomized to Sham	115 patients	34 patients
Inclusion Criteria	Age 18-75 years	Age 18-80 years	Age 18-80 years
	≥4 FI episodes over 14 days in patient diary	≥4 FI episodes over 28 days in patient diary	At least one FI episode weekly
	CCFIS≥10	CCFIS≥5	Miller score ≥6
	Solid or liquid FI episodes	Solid or liquid FI episodes	Solid or liquid FI episodes
	Failed conservative treatment	Failed conservative treatment	
Exclusion Criteria	Complete external sphincter disruption, Significant mucosal prolapse	Complete external sphincter disruption, Significant mucosal prolapse	Complete external sphincter disruption, Significant mucosal prolapse
Retreatment Criteria	Incontinent at one month after initial treatment and CCFIS ≥10	Incontinent at one month after initial treatment	Some subjective improvement but less than 50 % reduction in FI episodes

The Pivotal Study is the primary data set that demonstrates the safety and effectiveness of Solesta. The Open-Label and Proof-of-Concept studies provide supporting evidence of safety and effectiveness.

Treatment Information

Pre-operative Bowel Preparation

Pre-treatment evacuation of the rectum was done with an enema in the majority of the patients in all 3 studies. A small number of patients received topical antiseptic cleansing at the discretion of the treating physician. Prophylactic antibiotics were administered to individual patients in the Pivotal study at the discretion of the treating investigator and only 15 patients at 3 sites received prophylactic antibiotics in this study. No patients in the Open-Label study received prophylactic antibiotics.

Treatment Procedure

The Solesta injection procedure was the same in all 3 studies. Treatment was administered in an out-patient setting without anesthesia. Four equally spaced injections were administered through an anoscope and placed about 5 mm proximal to the dentate line. Treatment volume was generally 4 x 1 mL per treatment session. A single re-treatment procedure was offered to patients with persistent fecal incontinence after approximately 1 month. If a patient received retreatment, the maximum total treatment dose was 8 mL (4 mL per treatment x 2 treatments). In the Pivotal study, the sham injection procedure consisted of using 4 separate syringes to pierce the mucosa. The syringes were held in place for the same amount of time as Solesta injection: however, nothing was injected.

Table 5: Related Adverse Events (Including Serious AEs) by Time Interval of Event Onset Experienced by at Least 2 Patients Following Blinded or Open-Label Treatment with Solesta through Month 36 in the Pivotal Study. MedDRA Preferred Term. Safety Population (n=197)

	☐ 1st Solesta injection	☐ 2nd Solesta injection (at 1 month)					
MedDRA Preferred Term	**1st Solesta injection - 48 hours (N = 197) n (%)**	**>48 hours - 7 days (N = 197) n (%)**	**>7 days - 1 month (N = 197) n (%)**	**>1 month - 2 months (N = 197) n (%)**	**>2 months - 6 months (N = 197) n (%)**	**>6 months - 36 months (N = 194) n (%)**	**>36 months (N = 117) n (%)**
Proctalgia	17 (8.6%)	2 (1.0%)	7 (3.6%)	12 (6.1%)	1 (0.5%)	3 (1.5%)	0
Injection site hemorrhage	5 (2.5%)	0	3 (1.5%)	6 (3.0%)	3 (1.5%)	0	0
Rectal hemorrhage	2 (1.0%)	1 (0.5%)	2 (1.0%)	6 (3.0%)	2 (1.0%)	2 (1.0%)	0
Pyrexia	7 (3.6%)	0	2 (1.0%)	5 (2.5%)	0	0	0
Diarrhea	0	1 (0.5%)	3 (1.5%)	3 (1.5%)	1 (0.5%)	2 (1.0%)	0
Injection site pain	6 (3.0%)	0	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0
Anorectal discomfort	3 (1.5%)	0	2 (1.0%)	2 (1.0%)	2 (1.0%)	0	0
Anal hemorrhage	4 (2.0%)	0	1 (0.5%)	3 (1.5%)	1 (0.5%)	0	0
Rectal discharge	2 (1.0%)	0	1 (0.5%)	4 (2.0%)	0	0	0
Proctitis	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	0	0
Anal prolapse	0	0	0	0	1 (0.5%)	2 (1.0%)	0
Constipation	0	0	0	2 (1.0%)	1 (0.5%)	0	0
Anal pruritus	0	0	1 (0.5%)	1 (0.5%)	0	1 (0.5%)	0
Abdominal pain lower	1 (0.5%)	0	0	0	1 (0.5%)	0	0
Defecation urgency	0	0	0	2 (1.0%)	0	0	0
Painful defecation	1 (0.5%)	0	0	1 (0.5%)	0	0	0
Rectal obstruction	1 (0.5%)	0	0	0	1 (0.5%)	0	0
Chills	3 (1.5%)	0	1 (0.5%)	0	0	0	0
Injection site nodule	0	0	0	0	0	3 (1.5%)	0
Pain	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Rectal abscess	1 (0.5%)	0	1 (0.5%)	1 (0.5%)	0	0	0
Anal fissure	0	0	0	1 (0.5%)	0	1 (0.5%)	0
Rectovaginal septum abscess	0	0	0	0	0	1 (0.5%)	1 (0.9%)
Dyspareunia	0	0	0	0	2 (1.0%)	0	0
Alopecia	0	0	0	1 (0.5%)	1 (0.5%)	0	0

Notes: The following treatment-related adverse events were reported for 1 patient each: abdominal discomfort, abdominal distension, abdominal pain, abdominal rigidity, fecal incontinence, hard feces, gastrointestinal motility disorder, gastrointestinal pain, hemorrhoids, intestinal mass, nausea, rectal spasm, device dislocation, fatigue, implant site cyst, injection site inflammation, injection site irritation, injection site swelling, pelvic mass, anal abscess, *Escherichia coli* bacteremia, injection site pustule, mucosal excoriation, c-reactive protein increased, back pain, musculoskeletal pain, urinary retention, genital prolapse, perineal pain, vaginal discharge, vulvovaginal pain, cold sweat, and dermatitis.
The down arrow symbol (☐) indicates the timing of Solesta injections. Greater than 80% of subjects had 2 injections with Solesta (initial treatment and re-treatment approximately 1 month later).

Effectiveness

Primary Efficacy Objective - Pivotal Study

The Pivotal study included a primary efficacy objective composed of 3 parts. All 3 parts of the primary objective were met. The study was only powered for the primary endpoint and was not designed or powered to demonstrate a statistical difference between Solesta and Sham for the secondary efficacy endpoints.

Superiority was shown for Solesta (53.2%) versus Sham (30.7%) at 6 months (p=0.004; logistic regression), as illustrated in Figure 1, based on analysis of proportion Responder$_{50}$. Responder$_{50}$, defined as proportion of patients with a ≥ 50% reduction in number of incontinence episodes compared to baseline, has been used to objectively evaluate response to treatments for FI in other studies.

The second success criterion required that the results achieve a pre-specified minimum level of responders in the treatment group as defined by a lower confidence limit (LCL) of at least 35%. The LCL of the 95% confidence interval of the proportion Responder$_{50}$ at 6 months was 40.2%, as illustrated in Figure 2.

Safety Data

The safety evaluation of Solesta in the treatment of fecal incontinence (FI) is based on the results from the Pivotal clinical study, and is supported by the Open-Label multicenter clinical study and one single site Proof-of-Concept study. The analysis of safety was based on the safety cohort of all 206 patients treated in the Pivotal study with either Solesta or Sham. During the 6-month blinded phase (n = 136 in the Solesta group and n = 70 in the Sham group), treatment-emergent adverse events were experienced by 72% of the Solesta-treated patients and 60% of Sham-treated patients. Table 3 provides an overview of treatment-emergent adverse events during the 6-month blinded phase.

Table 3: Overview of Adverse Events during the 6-Month Blinded Phase of the Pivotal Study

	Solesta (n = 136) n (%)	Sham (n = 70) n (%)
Any treatment-emergent adverse event	98 (72.1)	42 (60.0)
Severe treatment-emergent adverse events	6 (4.4)	1 (1.4)
Serious treatment-emergent adverse events	7 (5.1)	2 (2.9)
Treatment-emergent adverse events considered related to study treatment by the investigator (treatment-related adverse events)	66 (48.5)	19 (27.1)
Serious treatment-related adverse events[a]	2 (1.5)	0

[a] Serious treatment-related adverse events were one case of *E. coli* bacteremia and one case of rectal abscess. A third patient experienced a serious treatment-related adverse event of rectal abscess during the open phase.

Safety data for Solesta are available from 359 treatments in 197 total patients followed for up to 36 months post treatment during the blinded and open phases of the Pivotal study (ie, the long-term population, including 136 patients who received Solesta during the blinded phase and an additional 61 patients who received Solesta during the open phase). Greater than 80% of subjects had 2 injections with Solesta (initial treatment and re-treatment approximately 1 month later); 113 of 136 patients (83.1%) received 2 Solesta injections during the blinded phase and 49 of 61 patients (80.3%) received 2 Solesta injections during the open phase. At least 1 treatment-emergent adverse event was experienced by 87% of patients in the long-term population. Severe treatment-emergent adverse events were reported for 12% of patients. For the subgroup of 61 patients who received Solesta at the start of the open phase, treatment-emergent AEs were experienced by 85% of patients and severe treatment-emergent adverse events were reported for 12% of patients.

In the long-term population, treatment-related adverse events (ie, treatment-emergent adverse events considered by the investigator to be related to Solesta injection) were experienced by 104 of 197 patients (53%) up to 36 months after treatment. For the subgroup of 61 patients who received Solesta at the start of the open phase, 31 of 61 (51%) had treatment-related adverse events during follow-up. Three (3) of 197 patients (1.5%) had treatment-related adverse events that were deemed serious by the investigators. These serious treatment-related adverse events include: one subject with *E. coli* bacteremia who presented with an ongoing urinary tract infection, prostatic hypertrophy, and possible upper respiratory tract infection, and 2 subjects with rectal abscess. The event of *E. coli* bacteremia and one event of rectal abscess occurred during the blinded phase; the other event of rectal abscess occurred during the open phase. These serious treatment-related adverse events resolved following treatment without sequelae within 35 days of event onset. The times from injection to event onset and other details of the 3 serious treatment-related adverse events are shown in Table 4.

Table 4: Serious Treatment-Related Adverse Events during the Blinded or Open Phases (up to 36 months post treatment)

Event	Treatment group	Intensity	Time from injection to event onset	Event Duration	Outcome
Escherichia coli bacteremia[a]	Solesta treatment - blinded phase	Moderate	0.5 days post first injection	35 days	Recovered
Rectal abscess[a]	Solesta treatment - blinded phase	Mild	2 days post second injection	5 days	Recovered
Rectal abscess[b]	Solesta treatment - open phase	Severe	4.5 months post second injection	5 days	Recovered

[a] These events occurred during the blinded phase.
[b] This event occurred during the open phase.

Overall, 96% of treatment-related adverse events required no intervention or required medical or simple non-invasive interventions, including application of local pressure, silicone ointment, water irrigation, and warm baths. Ten (10) treatment-related adverse events required more invasive procedures, as follows (with time from injection to event onset in parentheses): 6 cases of perianal drainage or incision and drainage of abscesses (2, 3, 15, 140, 1000, and 1053 days post injection, respectively), 1 case of lancing of a hemorrhoid (1 day post injection), 1 case of a Kenalog injection in a pre-existing anal scar (255 days post injection), 1 case of rubber band ligation of an anal prolapse (288 days post injection), and 1 case of rectovaginal cyst removal (594 days post injection). These events requiring intervention were considered by the investigator to be moderate or mild, with the exception of 1 severe case (nonserious) of rectal abscess (event onset 3 days after injection) that required drainage.

As shown in Table 5, the most frequent treatment-related adverse events following Solesta treatment pertained to post-treatment proctalgia, minor anal or rectal bleeding, post-treatment fever, abdominal complaints (such as diarrhea and constipation), and events potentially related to peri-operative infection. Most of these treatment-related adverse events were experienced soon after injection with Solesta; the highest incidence occurred during the 48-hour interval following the first injection. The onset of treatment-related adverse events, such as proctalgia, were also relatively frequent from > 1 month to 2 months post first injection; this result is consistent with re-injection of study treatment for most patients at 1 month post first injection (161 of 197 patients received a second injection at 1 month) in the Pivotal study. All of the events shown in Table 5 resolved during follow-up with the exception of one mild event of injection site nodule that was considered chronic/stable.

Combined with the supportive studies, a total of 346 patients received 566 treatments with Solesta. All three studies utilized similar inclusion/exclusion criteria and all three studies used exactly the same procedure for administering Solesta. The multi-center Open-Label study demonstrated similar safety results as the Pivotal study. A total of 163 AEs were reported by 71 of the 115 patients treated with Solesta in the Open-Label study. Of these AEs, 79 AEs reported by 44 patients (38%) were assessed by the investigators to be related to the study treatment. Thus, the incidence of treatment-related AEs per total number of performed treatments was 51.3% (79 events/154 treatments). Similar to the Pivotal study, the 5 most frequently reported types of treatment-related AEs were proctalgia, pyrexia, constipation, diarrhea and injection site pain. Six (6) treatment-related AEs reported in 4 patients were classified as serious in the study. Three (3) of these serious and treatment-related adverse events were cases of abscess reported by 3 patients and the remaining 3 were reported by a single patient who had a rectal prolapse with concurrent rectal bleeding and pain. In this latter case, tissues surrounding a Solesta bulge had prolapsed downwards in the anal canal and the Solesta bulge was excised in surgery.

In the Proof-of-Concept study, 34 patients were treated in the study and 33 patients were followed for 24 months. In total, 53 treatments with Solesta were administered in the study. These patients experienced a total of 86 treatment-related adverse events that were reported by 29 patients. No treatment-related adverse event was reported as serious. The duration was 1-4 days for most events and all events were resolved within 1 week. No adverse events occurred after month 12. One (1) patient gave birth to a healthy child approximately 18 months after treatment and the delivery was a normal vaginal delivery. The observed adverse events were similar to those seen in the Pivotal study.

Secondary Endpoints for Pivotal and Supporting Studies

The following secondary endpoints were evaluated in the three clinical studies:

- Fecal incontinence episodes
- Fecal incontinence-free days
- Fecal Incontinence Quality of Life (FIQL) assessment
- Cleveland Clinic Florida Incontinence Score (CCFIS) or Miller Score

Fecal Incontinence Episodes

In the Pivotal study, reductions in number of FI episodes from baseline at both 3 and 6 months were observed in both the Solesta and Sham treatment groups. For the Solesta group the median FI episodes were shown to decrease from 15 episodes at baseline to 7.2 episodes at 6 months and 6.2 episodes at 12 months. For the Sham group the median FI episodes were shown to decrease from 12.5 episodes at baseline to 10.0 episodes at 6 months (see Table 7). Both the Solesta and Sham groups showed a change from baseline at 6 months, and the change from baseline in the Solesta group was larger than that observed for the Sham group. Similar reductions from baseline with Solesta treatment were observed in the Open-Label study and the Proof-of-Concept study.

Figure 3 shows the sustained improvement in Responder$_{50}$ analysis and reduction in fecal incontinence episodes over 36 months in the Pivotal study for the Solesta group only.

Table 7: Median Number of Fecal Incontinence Episodes/14 Days for Each Treatment Group and Change from Baseline to 6 Months. As Observed. Last Observation Carried Forward (LOCF). ITT population (n=206 patients: Pivotal Study)

Number of episodes	Solesta (n=136) Median	Sham (n=70) Median	Difference in median changes between groups (Solesta-Sham)
Baseline	15.0	12.5	
6 months	7.2	10.0	
Δ from baseline	-6.0	-3.0	-3.0
% Δ from baseline	-50.6	-22.6	-28.0

Figure 1. Comparison of Proportion Responder$_{50}$ at 6 Months

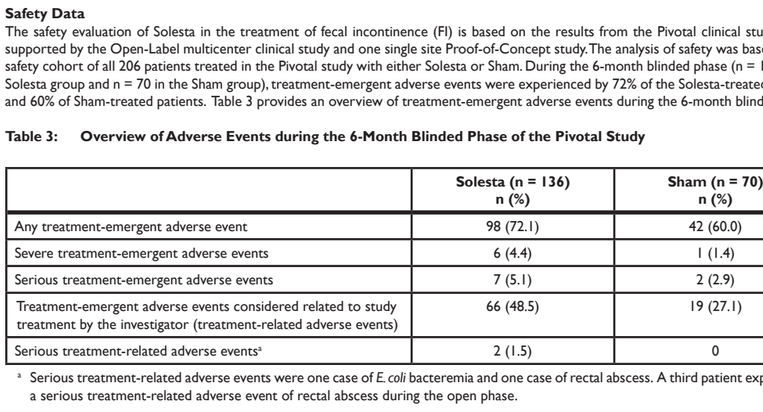
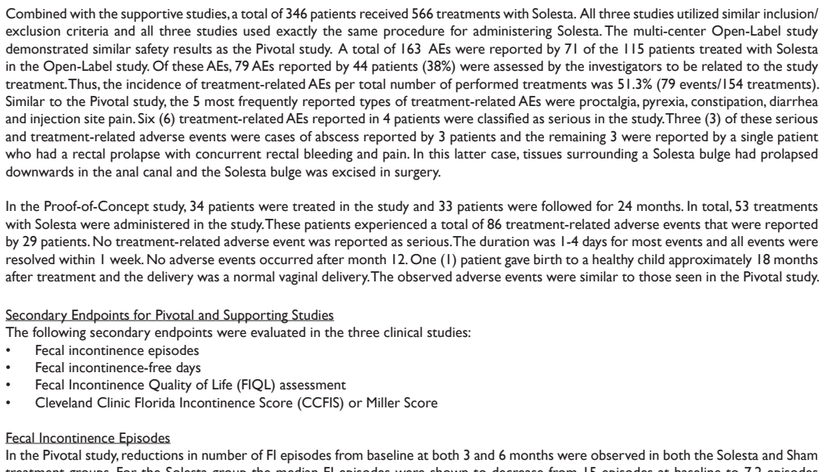


Figure 2. Solesta Proportion Responders at 6 and 12 Months

* Responder$_{50}$ LCL = 40.2 % > 35 %
** Responder$_{25}$ LCL = 61.4 % > 50 %

Figure 3. Median Number of FI Episodes and Proportion Responder$_{50}$ at Each Follow Up Time Point in the Pivotal Study. Solesta ITT Population (n=136)



Primary Endpoint Pivotal and Supporting Studies

All three studies show durability of the treatment effect to 24 months as evidenced by the proportion Responder$_{50}$. As shown in Table 6 the proportion Responder$_{50}$ at 6, 12 and 24 months were similar across all three studies. In addition, the Pivotal study showed durability of the treatment effect to 36 months.

Table 6: Summary of Proportion of Responder$_{50}$ at 6,12, 24 and 36 Months with Solesta Treatment.

Proportion Responder$_{50}$ [95% CI]	Pivotal study (ITT, PIM [6 month time point]; ITT, LOCF [12, 24, and 36 month time points])[a]	Open-Label Study (ITT, OC)	Proof-of-Concept Study (OC)
6 months	53.2% [40.2–65.8] n= 136	57.1% [47.3–66.9] n=98	44.1% [27.4–60.8] n=34
12 months	57.4% [49.0–65.7] n=136	64.4% [54.3–74.4] n=87	55.9% [39.2–72.6] n=34
24 months	54.4% [46.0-62.8] n = 136	62.7% [51.7-73.6] n=75	59.4% [42.4–76.4] n=32
36 months	52.2% [43.8-60.6] n=136	N/A	N/A

a The responder$_{50}$ proportion at 6 months in the ITT population was determined from the primary imputation model and is the same as shown in Figure 1. The responder$_{50}$ proportions at 12, 24, and 36 months in the ITT population were determined by the LOCF method. The responder$_{50}$ proportion at 6 months by the LOCF method was 52.2% [43.8-60.6].
CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; PIM = primary imputation model; OC = observed cases; n = number of patients

Fecal Incontinence-free days

In all three studies, an increase in number of fecal incontinence-free days was observed with Solesta treatment. In the Pivotal study at 6 months, both the Solesta and Sham treatment groups experienced an increase in number of incontinence free days from their pre-treatment baseline values of 4.4 days and 4.8 days, respectively. However, the Solesta group demonstrated an increase of 3.1 fecal incontinence-free days when compared to the Sham group increase of 2.0 days. At 12 months, the increase in number of fecal incontinence-free days in the Solesta group was maintained at 3.4 days. Similar increases in number of fecal incontinence-free days with Solesta treatment were shown in the Open-Label study and the Proof-of-Concept study.

Fecal Incontinence Quality of Life assessment (FIQL)

The FIQL scale is a validated tool that is specifically designed to assess the impact of FI on a patient's quality of life. In the blinded phase of the Pivotal study, improvement in FIQL scores compared to baseline was observed in both the Solesta and Sham groups at 6 months. The change from baseline score was greater in the Solesta group than the Sham group in all four domains: Lifestyle (Δ=0.22), Coping/Behavior (Δ=0.25), Depression/Self perception (Δ=0.09) and Embarrassment domains (Δ=0.16), (see Table 8). In the Open-Label study, FIQL scores showed a similar improvement. The Proof-of-Concept study did not evaluate FIQL.

Cleveland Clinic Florida Incontinence Score (CCFIS)

The CCFIS is a validated measure of the impact of FI on patients. In the pivotal study, in both the Solesta and Sham groups, the CCFIS was improved as compared to baseline at 6 months. The difference at 6 months in mean change from baseline between the Solesta group and the Sham group was small (see Table 8). Solesta showed improvements from baseline at 12 months in both the Pivotal study and the Open-Label study.

The Proof-of-Concept study did not incorporate CCFIS but instead used the Miller Score, another assessment tool for FI. The Miller Score is based on a subject interview using standardized questions regarding incidence and type of incontinence (solid, liquid or gas). Improvements from baseline and sustained improvements were shown at 6, 12, and 24 months.

Table 8: Secondary Efficacy Evaluations of Difference in Change from Baseline Between Solesta and Sham at 6 Months. LOCF. ITT Population (n=206 Patients: Pivotal Study)

Secondary endpoints	Score/Scale range	Estimate of mean change from baseline		Estimate of difference (95% CI)
		Solesta	Sham	
Fecal Incontinence Quality of Life (FIQL) scale (higher score = increased QoL)				
Lifestyle*	1-4	0.33	0.11	0.22 (0.04:0.40)
Coping/Behavior*	1-4	0.44	0.19	0.25 (0.08:0.43)
Depression/Self perception*	1-6	0.27	0.18	0.09 (-0.08:0.26)
Embarrassment*	1-4	0.53	0.38	0.16 (-0.05:0.36)
Cleveland Clinic Florida Incontinence Score (CCFIS)				
CCFIS score†	0 = continent; 20 = total incontinence	-3.06	-2.85	-0.21 (-1.15:0.72)

* Positive value indicates improvement; † Negative value indicate improvement

PATIENT COUNSELING INFORMATION

The patient should be advised that Solesta treatment is not effective for all patients with fecal incontinence and that repeat treatment might be required for treatment effect. It should also be made clear to the patient that the available clinical study data are not sufficient to predict in whom Solesta treatment will be effective. The patient should be informed about post-treatment care and potential adverse events. The patient should also be made aware that the implants might be detected during future anorectal examinations and radiographic imaging of the pelvis. Patients should be instructed to inform all future treating physicians about the presence of Solesta gel.

If there should be a need for future surgery (e.g., hemorrhoidectomy) the Solesta implant can be resected.

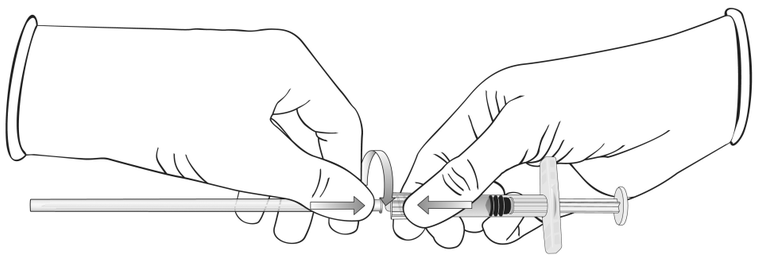
DIRECTIONS FOR USE

Solesta should be administered by qualified physicians with experience in the treatment of anorectal conditions and who have successfully completed a comprehensive training and certification program in the Solesta injection procedure. Solesta should only be used after a thorough physical evaluation of the patient to exclude treatable underlying disorders.

For the safe use of Solesta it is important that a new sterile needle is properly assembled and tightly fastened to each syringe.

Please note that the Luer-lock adapter is snapped onto the syringe and held in place with friction only. It can rotate freely or be pulled off should enough force be applied. Because of this it is recommended that the thumb and forefinger be held firmly around the Luer-lock adapter on the glass syringe while attaching the needle to the syringe. DO NOT attach the needle by holding onto the glass barrel of the syringe. To facilitate proper threading/fastening of the needle hub and Luer-lock adapter, please firmly push and rotate the needle hub into the Luer-lock adapter as illustrated in Figure 4.

Figure 4: Proper threading/fastening of the needle hub and Luer-lock adapter

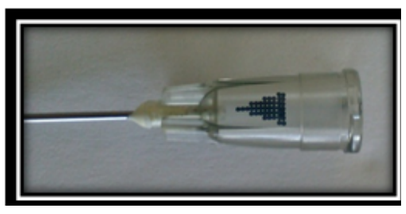


To avoid any interruption in patient treatment or the need to repeat a procedure because of leakage, or accidental contamination or damage of a syringe or needle, it is recommended that extra Solesta cartons be kept in inventory.

Method of Administration

1. The treatment is administered as an outpatient procedure without anesthesia.
2. Prior to treatment, the rectum should be evacuated with an enema. The enema should be given immediately prior to the procedure to ensure evacuation of the anorectum. Additional cleansing of the injection area with an antiseptic may be performed prior to injection.
3. Use of prophylactic antibiotics is recommended.
4. Four Solesta syringes should be made ready with mounted needles under aseptic conditions. Have small swabs and suction prepared and ready for use.
5. The patient is placed in the left lateral position, and a lubricated anoscope is inserted. The obturator is removed and the anoscope withdrawn so that the dentate line is identified.
6. There is a triangular mark on the needle hub that provides the orientation of the needle bevel to ensure the bevel is facing the lumen when the needle is inserted (Figure 5).

Figure 5: Mark Indicating Needle Bevel Orientation



7. The four injections are to be given in the following order: posterior, left lateral, anterior, and right lateral.
8. The injections should be performed slowly to avoid stress on the Luer-lock connection and allow the tissue to adapt to the injected gel.
9. Under direct vision, the mucosa is penetrated, approximately 5 mm proximal to the dentate line. The needle is advanced a further 5 mm at approximately 30° to the axis of the rectum. If the patient indicates pain at the puncture, the injection site should be adjusted a few mm in the cephalic direction. If the puncture is painless, 1 mL of Solesta is injected in the deep submucosal layer. After injection, the needle should be kept in position for 15-30 seconds to minimize leakage of Solesta.
10. The injection is to be repeated at the remaining three injection sites. A new needle should be used for each syringe and injection site.
11. After completion of the 4 injections, the anoscope is extracted and the patient may rise. The patient should be instructed to rest at the clinic for approximately 60 minutes.
12. If no bleeding or other treatment related symptoms are observed during this time, the patient can be allowed to leave the clinic.
13. Confirming placement of Solesta gel by imaging may be of benefit.

Post-treatment care

1. The patient should be instructed to avoid taking hot baths during the first 24 hours post-treatment.
2. The patient should be informed of the risk of infections and bleeding.
3. The patient should be instructed to contact the clinic or physician's office immediately if symptoms of rectal bleeding, bloody diarrhea, fever, tenesmus or problems with urinating occur.
4. Anti-diarrheal drugs should not be used for one week after treatment.
5. Stool softeners may be used until the first defecation occurs.
6. Analgesics other than Non-steroidal Anti-inflammatory Drugs (NSAIDs) may be prescribed, if needed.
7. The patient should be instructed to:
   - Avoid physical activity for 24 hours
   - Avoid sexual intercourse and strenuous physical activity for one week (e.g., horse back riding, bicycling and jogging, etc.)
   - Avoid anal manipulation for one month (e.g., insertion of suppositories or enemas and rectal temperature recording)

Re-treatment procedure

1. If the patient does not have an adequate response to Solesta after the first injection, a re-injection with a maximum of 4 mL Solesta can be performed, no sooner than 4 weeks after the first injection.
2. The re-treatment procedure and all pretreatment preparations are performed the same way as the initial treatment procedure. All pretreatment preparations and injection procedures should be performed as described in "Methods of Administration" above. However, the point of injection should be made in between the initial injections, shifted one-eighth of a turn (e.g., left posterolateral, left anterolateral, right anterolateral, and right posterolateral).

HOW SUPPLIED

Solesta is supplied in a glass syringe with a standard Luer-lock fitting containing 1 mL gel. Each syringe is terminally moist heat sterilized in a pouch. Four pouches, each containing one syringe are packed in a carton together with four Steriject® needles (21G x 4¾ inches, 0.80 mm x 120 mm), patient record labels and a package insert. The needles are sterilized by gamma irradiation.

STORAGE

Store at a temperature up to 25°C (77°F) and protect from sunlight and freezing.

Manufactured for:

Salix Pharmaceuticals, a subsidiary of Valeant Pharmaceuticals International,
Rochester, NY 14609 USA

For product information, adverse event reports, and product complaint reports, please contact:

Salix Product Information Call Center
Phone: 1-800-508-0024
Fax: 1-510-595-8183
E-mail: Salix@medcomsol.com

Manufactured by:

Q-Med AB
Seminariegatan 21
SE-752 28 Uppsala
Sweden

Made in Sweden

Rev. 04/2016
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