LACRIFILL® Canalicular Gel
Instructions for Use

Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

DESCRIPTION

LACRIFILL® Canalicular Gel consists of a transparent and sterile hydrogel of hyaluronic acid cross-linked with 1,4-butanediol diglycidyl ether (BDDE) in a physiological buffer. The gel is contained in a syringe which is packaged in a sealed tray. The device is packaged for single patient use.

The syringe is filled to 0.6 mL with gel to accommodate insertion of LACRIFILL into both inferior canaliculi of a single patient.

INDICATIONS FOR USE

LACRIFILL is intended to block tear drainage by occlusion of the canalicular system. It is indicated for use, for up to 6 months, in patients experiencing dry eye symptoms.

CONTRAINDICATIONS

LACRIFILL is contraindicated for patients experiencing epiphora, inflammation of the eye lid, and tearing secondary to dacryocystitis with mucopurulent discharge and any other active ocular or periocular infection, those who are allergic to hyaluronic acid or to the specific device material, and those who have known lacrimal outflow obstruction.

WARNINGS

- As with any procedure, use of LACRIFILL carries a risk of infection. Standard precautions associated with injectable materials should be followed. Should an infection occur, flush the plug from the canaliculus.
- If the patient experiences irritation, infection, or epiphora after insertion of LACRIFILL, the plug should be removed.
- In the pivotal clinical study, the safety and effectiveness of LACRIFILL was characterized over a 6-month period. The safety and effectiveness of the device for longer periods of use has not been established. Therefore, LACRIFILL should be used for no more than 6 months. After 6 months, LACRIFILL should be removed by thorough lacrimal irrigation.
- It should be noted that the ease of LACRIFILL removal by irrigation was not robustly evaluated in the pivotal clinical trial. When removing LACRIFILL, ensure that punctal irrigation is sufficiently thorough. If irrigation does not remove the plug, lacrimal probing or surgical exploration may be needed.
- To minimize the risks of potential complications, LACRIFILL should only be inserted by health care practitioners who have appropriate training and experience, and who are knowledgeable about the anatomy at and around the punctum and canaliculus.
- Patency of the canaliculus should be determined prior to insertion of LACRIFILL. Do not insert LACRIFILL if the canaliculus is not patent. Care should be used not to perforate the punctum or canaliculus during the insertion of the LACRIFILL. Perforation may cause pain and increased risk of infection. If perforation occurs, delay the insertion of the plug until the wound heals.

PRECAUTIONS

- LACRIFILL is a clear, colorless gel without visible particulates. If the contents of a syringe show signs of separation and/or appear cloudy or colored, do not use the syringe; notify Nordic Pharma, Inc. at 1-844-267-4641.
- LACRIFILL is provided STERILE for single patient use only.
- Do not resterilize the syringe containing the gel.
- Use the device prior to the expiration date printed on the label.
- Prior to use, inspect the package and device to verify that there is no damage to the device or package. Do not use the device if the device or packaging appears open or damaged.
- Failure to comply with the cannula attachment instructions could result in cannula disengagement and/or product leakage at the Luer lock and cannula hub connection.
- As with any punctal or canalicular plug, LACRIFILL may enhance the effects of ocular medications used on the eye. Depending on the type of medications being used, dosage may need to be adjusted accordingly.
- After use, dispose of the syringe in accordance with accepted medical practice and applicable local, state, and federal requirements. If a reusable Bailey lacrimal cannula has been used, it should be cleaned and resterilized using standard procedures consistent with the cannula manufacturer's instructions for use and institutional procedures.
- The clinical performance of LACRIFILL has not been established in the following conditions/patient populations:
  - Pregnancy
  - Pediatric patients (i.e., under 22 years of age)
  - Use of ophthalmic cyclosporine (Restasis) within 6 months or lifitegrast (Xiidra) within 3 months
  - Corneal transplant
  - Ocular surgery (such as cataract surgery or LASIK) within six months
  - Current systemic infection, uncontrolled autoimmune disease, uncontrolled immunodeficiency disease
  - Significant corneal or conjunctival scarring, pterygium or nodular pinguecula; current ocular infection (except mild blepharitis), conjunctivitis or inflammation not associated with dry eye; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; history of ocular herpetic infection; evidence of keratoconus; lid or lacrimal cancer
  - Active severe systemic allergy, seasonal allergies, rhinitis or sinusitis requiring treatment (i.e., antihistamines, decongestants, oral or aerosol steroids)
  - Use of steroids, including administration by systemic or topical ocular routes

POTENTIAL COMPLICATIONS

- Ocular discomfort or irritation
- Conjunctivitis
- Conjunctival injection
- Canaliculitis
- Dacryocystitis
- Subconjunctival hemorrhage
- Punctal stenosis
- Eyelid telangiectasia
- Eyelid edema
- Eyelid induration
- Eyelid erythema
- Eyelid discomfort
- Epiphora
- Clinically significant decrease (≥10 letters) in Best Corrected Distance Visual Acuity
- Clinically significant increase in corneal epithelial staining, e.g., an increase in corneal staining score of 2 or more in at least one corneal area or an increase in the sum for all corneal areas of 4 or more (using NEI grid and scale)

INSTRUCTIONS FOR USE:

Cannula Preparation

1. A sterile, disposable, or reusable 27-gauge Bailey cannula may be used with the gel-filled syringe. If a reusable Bailey cannula, such as a 27-gauge Bailey lacrimal cannula, Ambler Surgical part number SP190725-1 or equivalent, is to be used, the cannula should be cleaned and sterilized prior to use for insertion of the gel plug consistent with the cannula's instructions for use and institutional procedures.
2. Prior to punctal irrigation and insertion of LACRIFILL, a topical anesthetic agent should be instilled in the conjunctival sac for patient comfort. Punctal irrigation must demonstrate patent lacrimal drainage prior to insertion of LACRIFILL.
3. To prepare for insertion of the gel, open the box, inspect the packaging for any signs of damage, remove the tray containing the gel-filled syringe, and peel off tray cover. Do not use if packaging has been compromised or device has been damaged.
4. Remove the cap from the gel-filled syringe (Figure 1).

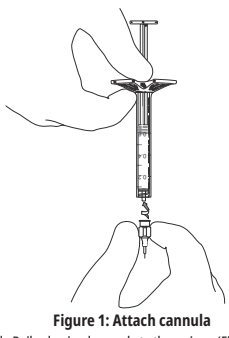

Figure 1: Attach cannula

5. Attach a sterile Bailey lacrimal cannula to the syringe (Figure 2). Ensure that the attachment is secure.

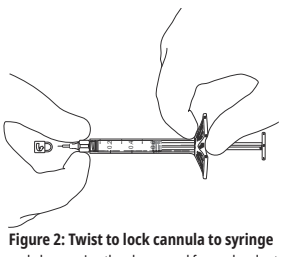

Figure 2: Twist to lock cannula to syringe

6. Prime the cannula by pressing the plunger rod forward and extrude 0.1 mL of gel through the Bailey lacrimal cannula (Figure 3). The volume of gel left in the syringe should be 0.5 mL.

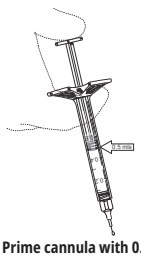

Figure 3: Prime cannula with 0.1 mL gel

Insertion

7. Place the tip of the Bailey lacrimal cannula into the lower punctum of the first eyelid and insert 0.2 mL of gel (Figure 4). The punctum may be dilated if necessary for introduction of the Bailey lacrimal cannula. Note: In approximately one-third of cases, gel extrusion from the upper punctum might be observed in which case excess gel can be irrigated from the ocular surface if it obscures the patient's vision.

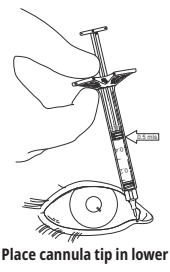

Figure 4: Place cannula tip in lower punctum

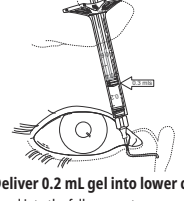

Figure 5: Deliver 0.2 mL gel into lower canaliculus

8. For insertion of the gel into the fellow punctum, purge the Bailey cannula with 0.1 mL of gel (the volume of gel left in the syringe should be 0.2 mL,) then repeat as illustrated in Figures 4 and 5 above.
9. Remove the Bailey lacrimal cannula from the syringe. If using a reusable cannula, clean and resterilize using standard procedures consistent with the cannula manufacturer's instructions for use and institutional procedures.
10. Discard the syringe, the disposable cannula if used, any remaining gel, and packaging in accordance with accepted medical practice and applicable local, state, and federal requirements.

Removal of the Plug

If irritation, infection, or bothersome epiphora is observed, LACRIFILL may be removed. To remove the plug, irrigate the plug from the canaliculus using a syringe filled with sterile saline. Attach a lacrimal cannula onto the syringe, insert the cannula into the canaliculus, and gently irrigate until LACRIFILL is removed from the canaliculus as evidenced by free flow of fluid through the lacrimal drainage system and/or the patient's report of swallowing or a fluid sensation in the nose or throat.

SUMMARY OF PIVOTAL CLINICAL STUDY

A prospective, multicenter, randomized, double masked, controlled clinical trial was performed to evaluate the clinical performance of LACRIFILL (canalicular gel) compared to the predicate device over 6 months of participant follow-up. Eligible participants age 22 or older with ocular signs and symptoms consistent with dry eye syndrome and with bilateral lacrimal drainage system patency as demonstrated by punctal irrigation were randomly assigned in a 2:1 ratio (LACRIFILL Canalicular Gel:Oasis Form Fit) to undergo bilateral implantation in the inferior canaliculus with LACRIFILL or the Oasis Form Fit plug. Participants had a baseline examination within 30 days prior to the initial treatment with either canalicular gel or control. Scheduled follow-up visits occurred at Week 1, Month 1, Month 3, and Month 6. All participants underwent plug removal via lacrimal irrigation at the 6-month visit (if it not already removed at an earlier timepoint).

Participant Disposition

157 participants were enrolled and randomized. The safety population included 157 participants (103 in the canalicular gel group, 54 in the control group). The intent-to-treat (ITT) population was comprised of 156 participants (103 in the canalicular gel group, 54 in the control group); one participant in the canalicular gel group did not have the device successfully applied. 151 participants comprised the per-protocol (PP) population (99 in the canalicular gel group, 52 in the control group). Exclusions from the PP cohort were comprised of three participants (3%) in the canalicular gel group and two (4%) from the control group had major protocol deviations. 151 participants (96.2%) completed the trial, and six (3.8%; four in the canalicular gel group, two in the control group) were discontinued.

Demography and Baseline Characteristics

The majority of participants (118/156, 75.6%) were women (74/102 [72.5%] in the canalicular gel group; 44/54 [81.5%] in the control group). The mean age was 62.9±11.66 years (range 26 to 84; mean age in the canalicular gel group 61.9±12.42 [range 26 to 84], mean age in control group 64.9±9.86 [range 47 to 82]). The majority of participants (125/156, 80.1%) identified as white (79/102 [77.5%] the canalicular gel group; 46/54 [85.2%] control group). 15 of 156 (9.6%) identified as Black or African-American (12/102 [11.8%] in the canalicular gel group; 3/54 [5.6%] in the control group). 13 of 156 participants identified as Asian (9/102 [8.8%] in the canalicular gel group; 4/54 [7.4%] in the control group). Two canalicular gel group participants identified as other race and one control-group participant identified has being of multiple races. The majority (147/156, 94.2%) did not identify as Hispanic or Latino (97/102 [95.1%] the canalicular gel group; 50/54 [92.6%]).

152 of 157 (96.8%) were previously documented with having dry eye syndrome (99/103 [96.1%] the canalicular gel group, 53/54 [98.1%] control group). 26 of 157 participants (16.6%) had previously undergone laser keratomileusis (20/103 [19.4%] the canalicular gel group; 6/54 [11.1%] control group) and 25 of 157 (15.9%) had previously undergone cataract extraction (18/103 [17.5%] the canalicular gel group; 7/54 [13.0%]). 31 of 157 (19.7%) had documented history of meibomian gland dysfunction (20/103 [19.4%] the canalicular gel group, 11/54 [20.4%] control group). 13 of 157 (8.3%) had documented history of blepharitis (11/103 [10.7%] the canalicular gel group, 2/54 [3.7%] control group). Baseline best-corrected distance visual acuity (BCDVA) was - 0.009±0.12 logMAR (range, -0.30 to 0.36 logMAR) in the right eye and 0.002±0.12 logMAR (range, -0.30 to 0.42 logMAR) in the left eye.

The baseline value for the anesthetized Schirmer's test was 5.5±2.71 mm (right eye; 5.5±2.75 mm [range, zero to 10 mm] the canalicular gel group, 5.6±2.67 mm [range, 1 to 10 mm] control group) and 5.3±3.01 mm (left eye; 5.2±3.05 mm [range, zero to 10 mm] the canalicular gel group, 5.4±2.97 mm [range, 1 to 10 mm] control group), range, zero to 10 mm for both eyes. Baseline mean tear meniscus heights were 0.915±1.57 mm (range, 0.05 to 8.67 mm) in the right eye (0.941±1.61 mm [range, 0.05 to 8.67 mm] the canalicular gel group, 0.866±1.52 [range, 0.08 to 7.67 mm] control group) and 0.866±1.4899 (range, 0.06 to 10.67 mm) in the left eye (0.914±1.62 mm [range, 0.10 to 10.67 mm] the canalicular gel group, 0.776±1.22 mm [range, 0.06 to 6.33 mm] control group). Baseline mean corneal fluorescein staining scores were 5.9±3.35 (range, 1 to 15) in the right eye (5.8±3.43 [range, 1 to 15] the canalicular gel group; 6.0±3.23 [range, 1 to 15] control group) and 5.9±3.17 in the left eye (5.9±3.25 [range, 1 to 15] the canalicular gel group; 6.1±3.03 [range, 1 to 15] control group). Baseline tear break-up time (TBUT) was 3.02±1.49 seconds (range, 0.17 to 11.25 seconds) in the right eye (2.98±1.51 seconds [range, 1.06 to 11.25 seconds] the canalicular gel group; 3.10±1.47 seconds [range, 0.17 to 6.74 seconds] control group).

Baseline mean total score on the Ocular Surface Disease Index© (OSDI) questionnaire was 48.0±16.38 (range, 25 to 93); 48.8±17.49 (range, 25 to 93) in the canalicular gel group, 46.4±14.07 (range, 25 to 79) in the control group. The baseline mean OSDI score for the ocular symptoms subscale (Items 1 through 5) was 42.4±18.09 (range, 10 to 95); 44.0±19.43 (range, 10 to 95) in the canalicular gel group and 39.4±14.97 (range, 10 to 70) in the control group. The baseline mean OSDI score for the vision-related functional subscale (Items 6 through 9) was 47.0±23.25 (range, zero to 100); 48.2±23.31 (range, zero to 100) in the canalicular gel group, 44.7±23.20 (range, zero to 88) in the control group. The baseline mean OSDI score for the environmental triggers subscale (Items 10 through 12) was 59.0±26.34 (range, zero to 100); 57.9±27.05 (range, zero to 100) in the canalicular gel group, 61.0±25.09 (range, zero to 100) in the control group.

Effectiveness Results Summary

At Month 3, for the right eye, the mean change in anesthetized Schirmer's test score was 3.40±7.54 mm (range, -7.0 to 30.0 mm) in the canalicular gel group (95% confidence interval [CI] 1.88-4.92 mm) and 1.78±5.44 mm (range, -7.0 to 21 mm) in the control group (95% CI 0.23-3.33 mm). For the left eye, the mean change in anesthetized Schirmer's test score was 3.38±7.005 mm (range, -8.0 to 31.0 mm) in the canalicular gel group (95% CI 1.97-4.79 mm) and 2.24±5.76 mm (range, -8.0 to 25.0 mm) in the control group (95% CI 0.60-3.88 mm). The LS mean between-group difference was 1.19±1.16 mm (95% CI -1.10 to 3.48 mm). At Month 3, 83 of 99 (83.8%) the canalicular gel group participants and 44 of 52 (84.6%) control group participants had an improvement in OSDI questionnaire score of at least 4.5 for those with moderate baseline symptoms or at least 7.3 for those with severe baseline symptoms. The mean proportional difference was -0.028 (95% CI -0.139 to 0.083).

Safety Results Summary

93 of 157 participants in the safety population (59.2%) reported a total of 242 adverse events (AEs). There were 238 TEAEs (treatment-emergent adverse events) reported. 59 participants (57.3%) in the canalicular gel group reported 152 TEAEs, 34 (63.0%) in the control group reported 86 TEAEs.

Most of the participants experienced TEAEs that were classified as mild (62 total [39.5%], 38 [36.9%] in the canalicular gel group and 24 [44.4%] in the control group). TEAEs in 27 participants [17.2%] (18 [17.5%] in the canalicular gel group and 9 [16.7%] in the control group) were reported as moderate severity. TEAEs in four participants [2.5%] (3 [2.9%] in the canalicular gel group, one [1.9%] in the control group) were classified as severe. One canalicular gel group participant reported experiencing ocular severe TEAEs (excessive tearing) classified as related to the study device; this event was resolved without sequelae.

Corneal staining was reported in 60 (38.2%) participants (36.9% in the canalicular gel group, 40.7% in the Oasis Plug group). Ocular pain was reported in 10 (6.4%) participants (9.7% in the canalicular gel group and zero in the control group). One case of presumed dacryocystitis was reported in the canalicular gel group. The event resolved without need for secondary surgical intervention. No dacryocystitis events were reported in the control group. Conjunctivitis events were reported in five canalicular gel group participants (4.9%) and one control-group participant (1.9%). Allergic blepharoconjunctivitis was reported in one canalicular gel group participant. Epiphora was reported in 7.8% (8/103) of the canalicular gel group and 5.6% (3/54) of the control group.

Two participants (one in each group) experienced AEs leading to premature treatment discontinuation. No participants experienced TEAEs leading to withdrawal. Three canalicular gel group participants (3/102, or 2.9%) and one control-group participant (1/54 or 1.9%) underwent an unplanned removal attempt due to an AE. There were two canalicular gel group participants who underwent unplanned device removal not due to an AE (voluntary withdrawals).

Questionnaires were administered to investigators to assess the ease of device insertion and the ease of device removal. On the insertion questionnaire, the mean response score to the question "How easy was it to insert the plugs?" (on a scale from 1 to 5, higher scores indicating greater difficulty) was

1.8±1.19 (range, 1 to 5) in the canalicular gel group and 1.4± 0.88 (range, 1 to 5) in the control group for the right eye; response scores were similar for the left eye. Difficulty inserting the device was reported for 26 canalicular gel group participants (25.5%) and two control-group participants (3.7%). Pain during the procedure as reported by the participant to the investigator (on a scale from 1 to 5, higher scores indicating more severe pain) were 1.4±0.77 (range, 1 to 4) in the canalicular gel group (right eyes) and 1.3±0.91 (range, 1 to 5) in the control group (right eyes; results similar for left eyes in both groups). The removal questionnaire consisted of four questions (regarding reflux from puncta during irrigation; how easy it was to irrigate the plug; any difficulties encountered during irrigation; patency of the lacrimal drainage system). Reflux from the right punctum during irrigation was observed in 31/101 (30.7%) and 15/51 (29.4%) of the canalicular gel- and control-group participants, respectively. Ease of irrigation (on a scale from 1 to 5, higher scores indicating greater difficulty) score was 1.9±1.10 (range, 1 to 5) in the canalicular gel group (right eyes) and 1.6±0.92 (range, 1 to 4) in the control group (right eyes; left eye results similar). Difficulties encountered during right punctum irrigation were reported in 8/101 (7.9%) canalicular gel participants and 2/51 (3.9%) of control participants (similar results were reported for the left punctum). Patency of the lacrimal drainage system was deemed re-established by the investigator in 100/101 canalicular gel eyes (both right and left; 99.0%) and 51/51 control eyes (both right and left; 100%). Resistance encountered during infusion of the irrigation solution was reported in eight canalicular gel and two control participants.

Study Conclusions

The clinical performance of the LACRIFILL was similar to that of the Oasis plug.

HOW SUPPLIED

LACRIFILL Canalicular Gel is supplied in a syringe containing 0.6 mL of gel for single patient use. The contents of the syringe are sterile. Do not resterilize. Do not use if packaging is open or damaged.

EXPIRATION DATING AND STORAGE REQUIREMENTS

LACRIFILL must be used prior to the expiration date on the package. Store at a temperature of 5°C/35 °F up to 25°C/77°F. Do not freeze. Protect from sunlight. Refrigeration is not required.

LACRIFILL is a clear, colorless gel without visible particulates. If the contents of a syringe show signs of separation and/or appear cloudy, do not use the syringe; notify Nordic Pharma, Inc. at 1-844-267-4641.

EXPLANATION OF SYMBOLS

REF	Catalog number
LOT	Batch code
	Use by date
	Manufacturer
STERILE	Sterile fluid path
5°C 25°C	Temperature limits for storage
	Consult instructions for use
	Do not use if package is damaged
Rx Only	Prescription Use Only
2	Single-patient use only
2 STERILIZE	Do not resterilize
	Protect from light sources

Manufactured for:
Nordic Pharma, Inc.
1205 Westlakes Drive, Suite 275, Berwyn, PA 19312

Manufactured by:
Symatese SAS
ZI les Troques, 69630 Chaponost, France

U.S. Pat. Nos. 8,979,821 and 9,504,605

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