Hylenex® recombinant (hyaluronidase human injection) in Subcutaneous Fluid Administration for Achieving Rehydration
Hylenex® recombinant (hyaluronidase human injection) Indication

Hylenex recombinant (hyaluronidase human injection) is a tissue modifier indicated as an adjuvant in subcutaneous fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs, and in subcutaneous urography for improving resorption of radiopaque agents.
**Hylenex® recombinant (hyaluronidase human injection) Important Safety Information**

- Hypersensitivity to hyaluronidase or any other ingredient in the formulation is a contraindication to the use of this product.
- Discontinue *Hylenex* recombinant (hyaluronidase human injection) if sensitization occurs.
- Hyaluronidase should not be used to enhance the absorption and dispersion of dopamine and/or alpha agonist drugs.
- Hyaluronidase should not be injected into or around an infected or acutely inflamed area because of the danger of spreading a localized infection.
- Hyaluronidase should not be used to reduce the swelling of bites or stings.
- Hyaluronidase should not be used for intravenous injections because the enzyme is rapidly inactivated.
- Furosemide, the benzodiazepines, and phenytoin have been found to be incompatible with hyaluronidase.
- Anaphylactic-like reactions following retrobulbar block or intravenous injections have occurred, rarely.
- Hyaluronidase should not be applied directly to the cornea.
Hylenex® recombinant (hyaluronidase human injection) Important Safety Information (cont)

The most frequently reported adverse experiences have been local injection site reactions, such as erythema and pain. Hyaluronidase has been reported to enhance the adverse events associated with co-administered drug products.

Patients receiving large doses of salicylates, cortisone, ACTH, estrogens or antihistamines may require larger amounts of hyaluronidase for equivalent dispersing effect, since these drugs apparently render tissues partly resistant to the action of hyaluronidase.

Edema has been reported most frequently in association with subcutaneous fluid administration. The rate and volume of subcutaneous fluid administration should not exceed those employed for intravenous infusion. As with all parenteral fluid therapy, use the same precautions for restoring fluid and electrolyte balance. Special care must be taken in pediatric patients to avoid overhydration by controlling the rate and total volume of infusion. When solutions devoid of inorganic electrolytes are given subcutaneously, hypovolemia may occur.
MOA video
Background

• Subcutaneous (SubQ) administration of fluids was common from 1900 to 1950
  • IV route first developed in the 50s
• SubQ fluids safe and effective in mild to moderate dehydration¹
• IV access may be difficult in dehydrated children and the elderly
• Recombinant human hyaluronidase (rHuPH20) is FDA approved in subcutaneous fluid administration for achieving hydration

INFUSE (INcreased Flow Utilizing SC-Enabled)

• Adult and Pediatric Hydration
  – INFUSE-Lactated Ringer’s Clinical Study
    • First clinical study to assess the safety, tolerability, and SC infusion flow rate of lactated Ringer’s solution with and without Hylenex recombinant. Study conducted from 11/2005-1/2006.
  – INFUSE-Pediatric Rehydration Study I
    • First clinical study to evaluate the safety, effectiveness, and ease of use of SC rehydration using Hylenex recombinant for the rehydration of pediatric patients with mild to moderate dehydration. Study conducted 8/2007-6/2008.
  – INFUSE-Pediatric Rehydration Study II
    • First clinical study to compare the safety, effectiveness, and ease of use of SC rehydration using Hylenex recombinant vs. IV for the rehydration of pediatric patients with mild to moderate dehydration. Study conducted 11/2008-12/2009.
INFUSE-LR: Study Design

• Objective
  – To compare flow rate, tolerability, and safety of gravity-infused SubQ fluid hydration \pm Hylanex® recombinant in healthy adults

• Methods
  – Double-blind, 2-stage, placebo-controlled (N = 54)
  – Stage 1 (N = 5): All received 1 mL Hylanex recombinant SubQ and saline placebo, followed by 400 mL LR
  – Stage 2 (N = 49): Multiple doses tested; however, N = 18 received Hylanex recombinant SubQ and saline placebo, followed by 400 mL LR. N = 16 in efficacy analysis.

• Endpoints
  – Primary: time to infuse 400 mL LR
  – Secondary included investigator-rated tolerability, subject-rated discomfort, and AEs

LR = lactated Ringer’s.
INFUSE-LR: Outcomes

- 4-fold greater flow rate and significantly fewer subjects with moderate to severe edema for Hylenex® recombinant versus placebo
- Subject-rated discomfort lower versus placebo (5.8 ±10.7 versus 9.6 ±15.3) on VAS ($P<.002$)

VAS = visual analog scale, on which 0 = no discomfort and 100 = worst discomfort.

**INFUSE-LR: All AEs Reported in >2 Subjects**

- AEs localized, mild to moderate; no severe or serious AEs
- Overall, subject and investigator preference for *Hylenex®* recombinant was 88% \((P=.002)\) and 94% \((P<.001)\), respectively

<table>
<thead>
<tr>
<th>MedDRA Soc/Preferred Term</th>
<th>Incidence* %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hylenex recombinant (n = 18)</strong></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>38.9</td>
</tr>
<tr>
<td>Infusion/injection/catheter site pain</td>
<td>27.8</td>
</tr>
<tr>
<td>Infusion/injection site burning</td>
<td>11.1</td>
</tr>
<tr>
<td>Injection site anesthesia</td>
<td>11.1</td>
</tr>
<tr>
<td>Infusion/catheter site erythema</td>
<td>5.6</td>
</tr>
<tr>
<td>Infusion site induration</td>
<td>0</td>
</tr>
<tr>
<td><strong>Placebo (n = 18)</strong></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>50.0</td>
</tr>
<tr>
<td>Infusion/injection/catheter site pain</td>
<td>38.9</td>
</tr>
<tr>
<td>Infusion/injection site burning</td>
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</tr>
<tr>
<td>Injection site anesthesia</td>
<td>5.6</td>
</tr>
<tr>
<td>Infusion/catheter site erythema</td>
<td>0</td>
</tr>
<tr>
<td>Infusion site induration</td>
<td>11.1</td>
</tr>
</tbody>
</table>

*From the time of initial exposure to study drug through the 28-day follow-up assessment.

INFUSE-Peds I: Study Design

• Objective
  – To assess the efficacy, safety, and utility of Hylenex\textsuperscript{®} recombinant-enabled SubQ rehydration in children with mild to moderate dehydration

• Methods
  – Phase IV, single-arm, pilot study
  – 51 patients (aged 2 months to 10 years) received 1 mL Hylenex recombinant SubQ, followed by 1-hour continuous infusion of 20 mL/kg isotonic fluid
  – Infusion continued ± electrolytes up to 72 h if needed

• Endpoints
  – Primary: Proportion of patients successfully rehydrated by SubQ infusion and discharged without need for alternative rehydration
  – Secondary included ease of use (eg, time from catheter placement to start of infusion, number of attempts needed for SubQ catheterization), and AEs

INFUSE-PEDS I: Endpoints of SubQ Infusions

- 100% had successful SubQ line placement on the first attempt
  - Approximately 10% of the catheters dislodged and required reinsertion
- 94.1% (48/51) of patients were clinically rehydrated via SubQ infusion
- Median time to infusion after catheter placement: 2 min (range, 0 to 15)
- Only 1 attempt needed for SubQ access in 90.2% (46/51) of patients
- Investigators rated the SubQ procedure as more effective (92%) and less difficult (90%) than IV infusion
- 90% of parents were “satisfied” or “very satisfied” with the procedure and 94% considered the SubQ procedure to be successful

### INFUSE-PEDS I: Infusion Site Pain on Day 1

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients With Objective Pain Rating Score* (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator-assessed</td>
<td></td>
</tr>
<tr>
<td>After Hylenex® recombinant (pre-infusion)</td>
<td>0</td>
</tr>
<tr>
<td>After infusion start (max score)</td>
<td>28 0 7 4 1 0 0</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-assessed</td>
<td></td>
</tr>
<tr>
<td>After Hylenex® recombinant (pre-infusion)</td>
<td>1</td>
</tr>
<tr>
<td>After infusion start (max score)</td>
<td>3 1 1 1 0</td>
</tr>
</tbody>
</table>

*Objective Pain Rating Scale used for patients aged <3 y, where 0 (none), 1, or 2 (worst) in face, legs, activity, cry, and consolability (FLACC) and score sums range from 0 to 10.

†FACES Pain Scale used for patients aged 3 to 10 years, where 0 = no hurt, 1= hurts a little bit, 2 = hurts a little more, 3 = hurts even more, 4 = hurts a whole lot, 5 = hurts worst.

The Objective Pain Rating Scale (OPRS) was used for children younger than 3 years (N=40). The OPRS, also known as FLACC (Face, Legs, Activity, Cry, Consolability), measures pain on a scale from 0 (none) to 10 (most).
PEDS II: Overview (cont)

• Objective
  – To evaluate whether Hylenex® recombinant-enabled subcutaneous fluid administration can be given safely and effectively, with volumes similar to those delivered IV, in children with mild to moderate dehydration

• Methods
  – Pediatric patients ≥1 month to 10 years of age with mild to moderate dehydration
  – Noninferiority study was powered to test that the mean volume infused via SubQ was ≥85% of the volume delivered via IV
  – A sample size of 74 patients per group would provide at least 80% power at the 1-sided 0.025 level of significance for establishing the noninferiority of Hylenex recombinant-enabled subcutaneous fluid administration compared with IV

INFUSE-Peds II CSR; data on file, Halozyme Therapeutics.
Peds II: Methods – Infusion Procedures

• rHFSC
  – Access with angiocatheter or butterfly
  – 150 USP *Hylenex®* recombinant given (1 mL)
  – 20 mL/kg isotonic fluid given over 1 hour
  – Hydration continued for up to 72 hours

• IV
  – Access with angiocatheter
  – 20 mL/kg isotonic fluid given over 1 hour
  – Hydration continued for up to 72 hours

\[rHFSC = \text{*Hylenex®* recombinant-enabled subcutaneous fluid administration.}\]
# PEDS II: Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>rHFSC (n = 73)</th>
<th>IV (n = 75)</th>
<th>Total (N = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, y</td>
<td>2.1 (1.72)</td>
<td>2.4 (2.07)</td>
<td>2.3 (1.91)</td>
</tr>
<tr>
<td>Age group, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo to &lt;1 y</td>
<td>23 (31.5)</td>
<td>12 (16)</td>
<td>35 (23.6)</td>
</tr>
<tr>
<td>1 y to &lt;2 y</td>
<td>20 (27.4)</td>
<td>28 (37.3)</td>
<td>48 (32.4)</td>
</tr>
<tr>
<td>≥2 y to &lt;3 y</td>
<td>17 (23.3)</td>
<td>18 (24)</td>
<td>35 (23.6)</td>
</tr>
<tr>
<td>≥3 y</td>
<td>13 (17.8)</td>
<td>17 (22.7)</td>
<td>30 (20.3)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (46.6)</td>
<td>39 (52)</td>
<td>73 (49.3)</td>
</tr>
<tr>
<td>Female</td>
<td>39 (53.4)</td>
<td>36 (48)</td>
<td>75 (50.7)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>25 (34.2)</td>
<td>22 (29.3)</td>
<td>47 (31.8)</td>
</tr>
<tr>
<td>White</td>
<td>39 (53.4)</td>
<td>40 (53.3)</td>
<td>79 (53.4)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (12.3)</td>
<td>13 (17.3)</td>
<td>22 (14.9)</td>
</tr>
<tr>
<td>Mean (SD) baseline weight, kg</td>
<td>11.8 (4.14)</td>
<td>12.9 (4.68)</td>
<td>12.4 (4.44)</td>
</tr>
<tr>
<td>Gorelick Dehydration Score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (1-2)</td>
<td>20 (27.4)</td>
<td>23 (30.7)</td>
<td>43 (29.1)</td>
</tr>
<tr>
<td>Moderate (3-6)</td>
<td>53 (72.6)</td>
<td>52 (69.3)</td>
<td>105 (70.9)</td>
</tr>
</tbody>
</table>

*rHFSC = Hylenex® recombinant-enabled subcutaneous fluid administration.*
rHFSC = Hylenex® recombinant-enabled subcutaneous fluid administration.
PEDS-II:
95% SubQ Needle Placement After 1 Stick

rHFSC = *Hylenex*® recombinant-enabled subcutaneous fluid administration; IV = intravenous.
rHFSC: 1 attempt, n = 69; 2 attempts, n = 4; 3 attempts, n = 0; >3 attempts, n = 0
IV: 1 attempt, n = 44; 2 attempts, n = 9; 3 attempts, n = 5; >3 attempts, n = 1; failure, n = 16
*Overall P<0.01 comparing distributions of rHFSC and IV groups (successes)
16 (21.3%) patients in the IV group did not achieve successful access. Additional needle sticks were required to initiate rescue therapy.

INFUSE-Peds II CSR; data on file, Halozyme Therapeutics.
PEDS-II: 100% SubQ Catheterization Success Across All Groups

rHFSC = Hylenex® recombinant-enabled subcutaneous fluid administration; IV = intravenous.

INFUSE-Peds II CSR; data on file, Halozyme Therapeutics.
PEDS II: Time to Treatment Initiation
(First Catheterization to Start of Infusion)

rHFSC: Median time = 3.5 minutes; IV: Median time = 11.8 minutes  *Overall P<0.0001.

rHFSC = Hylenex® recombinant-enabled subcutaneous fluid administration; IV = intravenous.
Peds II: Percent Rehydration Success Among All Randomized Patients

- In patients randomized to receive *Hyaluronidase human injection* facilitated SubQ rehydration who were successfully catheterized, 93.2% (68/73) were successfully rehydrated.

- In patients randomized to IV administration, 78.7% (59/75) had successful catheter placement; 69.3% (52/75) were successfully rehydrated.
• 93.2% (68/73) of patients in SubQ arm were successfully rehydrated in the ED
• 88.1% (52/59) of patients in IV arm were successfully rehydrated in the ED
# Peds II: Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Randomized to rHFSC (n = 73) Mean (95% CI)</th>
<th>Randomized to IV (n = 75) Mean (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration score improvement†</td>
<td>2.6 (2.9, 2.3)</td>
<td>2.2 (2.6, 1.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Weight change from baseline (kg)</td>
<td>0.3 (-0.3, 1.0)</td>
<td>0.5 (-0.6, 17.7)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

rHFSC = Hylenex® recombinant-enabled subcutaneous fluid administration; IV = intravenous.

*Null hypothesis tested: rHFSC<IV.
†Gorelick 10-item score.
• During the first hour of infusion, the mean flow rate of the infusion was similar for those receiving *Hylenex* recombinant-facilitated SubQ rehydration compared with those receiving IV-enabled rehydration*

• In successfully rehydrated patients who received hydration therapy for at least 1 hour and in whom weights were obtained.

INFUSE-Peds II CSR; data on file, Halozyme Therapeutics.
INFUSE-PEDS II: Total Volume Delivered in ED Was Similar Between SubQ and IV

- **Fluid Volume Infused**
  - **SubQ with Hylenex**
    - Mean Volume (mL): 334.3
    - Hospital stay: 365.0 mL
    - ED Only: 299.6 mL
  - **IV**
    - Mean Volume (mL): 464.8 mL
    - 165.2 mL

- **Statistical Significance**
  - P = 0.0325

- **Sample Sizes**
  - SubQ with Hylenex® recombinant: n = 73
  - IV: n = 75
INFUSE-PEDS II: Total Volume Delivered in ED Was Similar Between SubQ and IV (cont)

<table>
<thead>
<tr>
<th>All Randomized Patients</th>
<th>Randomized to rHFSC (n = 73) Mean (SD)</th>
<th>Randomized to IV (n = 75) Mean (SD)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total volume (mL) infused at a single infusion site (ED + inpatient)</td>
<td>365.0 (324.57)</td>
<td>455.8 (597.43)</td>
<td>0.51</td>
</tr>
<tr>
<td>Total volume (mL) (adjusted by duration)</td>
<td>406.7 (233.23)</td>
<td>413.7 (232.88)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total volume (mL) (ED only)</td>
<td>334.3 (226.40)</td>
<td>299.6 (252.33)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Note: For those patients who did not have the assigned type of infusion device (IV or SubQ) successfully placed (ie, the 16 IV-assigned patients who did not have successful placement of an IV device), the volume of IV fluid infused was imputed as 0 mL.

rHFSC = Hylenex® recombinant-enabled subcutaneous fluid administration; IV = intravenous.

*A P value of <0.05 is required to reject inferiority of rHFSC versus IV.
INFUSE-PEDS II: Total Volume Delivered in ED Was Similar Between Non-rescued SubQ and IV

Fluid Volume Infused

<table>
<thead>
<tr>
<th>Mean Volume (mL)</th>
<th>SubQ with Hylenex® recombinant (n = 73)</th>
<th>IV (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>365 mL</td>
<td>579.4 mL</td>
</tr>
<tr>
<td></td>
<td>334.3</td>
<td>380.8</td>
</tr>
<tr>
<td></td>
<td>30.7</td>
<td></td>
</tr>
</tbody>
</table>

Hospital stay

ED Only
INFUSE-PEDS II: Total Volume Delivered in ED Was Similar Between IV and SubQ (cont)

<table>
<thead>
<tr>
<th>Nonrescued Patients</th>
<th>Randomized to rHFSC (n = 73) Mean (SD)</th>
<th>Randomized to IV (n = 59) Mean (SD)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total volume (mL) infused at a single infusion site (ED + inpatient)</td>
<td>365.0 (324.57)</td>
<td>579.4 (618.49)</td>
<td>0.8915</td>
</tr>
<tr>
<td>Total volume (mL) (ED only)</td>
<td>334.3 (226.40)</td>
<td>380.8 (223.08)</td>
<td>0.5469</td>
</tr>
</tbody>
</table>

*rHFSC = Hylenex® recombinant-enabled subcutaneous fluid administration; IV = intravenous.

* A P value of <0.05 is required to reject inferiority of rHFSC versus IV.
## Adverse Events – Infusion Site Reactions

<table>
<thead>
<tr>
<th>Administration Site Conditions</th>
<th>rHFSC (n = 73) (^a)</th>
<th>IV (n = 75) (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infusion site reaction</td>
<td>73 (100.0)</td>
<td>63 (84.0)</td>
</tr>
<tr>
<td>Erythema(^b)</td>
<td>54 (74.0)</td>
<td>19 (25.3)</td>
</tr>
<tr>
<td>Edema(^c)</td>
<td>5 (6.8)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Pain(^d)</td>
<td>57 (78.1)</td>
<td>59 (78.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Swelling(^e)(^f)</td>
<td>59 (80.8)</td>
<td>16 (21.3)</td>
</tr>
<tr>
<td>Extravasation</td>
<td>0</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

\(^a\)Frequency and count based on treatment received.

All infusion-site reactions were mild except for the following: \(^b\)moderate (rHFSC [n = 4]; IV [n = 1]); \(^c\)moderate (rHFSC [n = 2]); \(^d\)moderate (rHFSC [n = 11]; IV [n = 9]); severe (rHFSC [n = 1]); \(^e\)moderate (rHFSC [n = 10]; IV [n = 1]); \(^f\)Swelling in rHFSC group due to infusion fluid and not inflammatory process.

\(rHFSC = \text{Hylenex}\textsuperscript{\textregistered}\text{ recombinant-enabled subcutaneous fluid administration; IV = intravenous.}\)
PEDS-II: Safety Summary

- All patients receiving rHFSC fluid administration (n = 73) experienced at least 1 infusion-site AE versus 63 (84%) of patients in the IV group (P<0.001)
- The majority of AEs were considered to be mild to moderate in severity. Seventy-three of 73 (100%) patients in the rHFSC group versus 64 of 75 (85.3%) in the IV group experienced administration-site adverse events or general disorders
- SAEs were reported in 8 patients (rHFSC, n = 3 and IV, n = 5). None were determined by the investigator to be related to study treatment.

rHFSC = Hylenex® recombinant-enabled subcutaneous fluid administration; IV = intravenous.
PEDS-II: Conclusions

- *Hylenex®* recombinant-enabled SubQ is a safe and effective alternative to the IV route for mild to moderate dehydration
- The primary efficacy outcome measures
  - Total (ED plus inpatient hospital stay) mean (SD) volume infused SubQ was 365.0 (SD = 324.57) mL over 3.1 hours versus 455.8 (SD = 597.43) mL over 6.6 hours for IV, which was insufficient to reject the hypothesis of noninferiority
- The difference in the mean duration of infusion resulted from hospital practices and treatment protocols
- When the ED data were analyzed separately, rHFSC and IV hydration were similar
  - SC: 334.3 mL (SD = 226.40) ($P<0.03$)
  - IV: 299.6 mL (SD = 252.33)

*rHFSC = Hylenex®* recombinant-enabled subcutaneous fluid administration; IV = intravenous.

INFUSE-Peds II CSR; data on file, Halozyme Therapeutics.
Summary

• *Hylenex* recombinant-enabled subcutaneous delivery of fluids is clinically proven to be a safe and effective alternative to the IV route in mild to moderate dehydration.

• Clinical studies demonstrated a 100% first stick catheter placement success rate.

• The subcutaneous route of administration enabled by *Hylenex* recombinant is clinically proven to save time in catheter insertion and fluid infusion.

• The *Hylenex* recombinant-enabled subcutaneous fluid delivery route is preferred over IV by parents, patients and caregivers.
HYLENEX recombinant
(hyaluronidase human injection)
150 USP units/mL

**INDICATIONS AND USAGE**
- HYLENEX recombinant is indicated as an adjunct in subcutaneous urography for improving resorption of radiopaque agents (1.3).
- HYLENEX recombinant is indicated as an adjuvant to increase the dispersion and absorption of other injected drugs.
- HYLENEX recombinant is indicated as an adjuvant in subcutaneous fluid administration for achieving hydration.

**WARNINGS AND PRECAUTIONS**
- Subcutaneous fluid administration: Inject 150 U HYLENEX recombinant prior to subcutaneous fluid administration. It will facilitate absorption of 1,000 mL or more of solution. The dosage of subcutaneous fluid administration is dependent upon the age, weight, and clinical condition of the patient as well as laboratory determinations. The rate and volume of subcutaneous fluid administration should not exceed those employed for intravenous infusion (2.1).
- In subcutaneous fluid administration, special care must be taken in pediatric patients to avoid over hydration by controlling the rate and volume of the infusion (2.1, 8.4, 14).

**USE IN SPECIFIC POPULATIONS**
- **Pediatric Use:** Clinical hydration requirements for children can be achieved through administration of subcutaneous fluids facilitated with HYLENEX recombinant. The dosage of subcutaneous fluids administered is dependent upon the age, weight, and clinical condition of the patient as well as laboratory determinations. For premature infants or during the neonatal period, the daily dosage should not exceed 25 mL/kg of body weight and the rate of administration should not be greater than 2 mL per minute. During subcutaneous fluid administration, special care must be taken in pediatric patients to avoid over hydration by controlling the rate and volume of the infusion (2.1, 8.4, 14).

**DRUG INTERACTIONS**
- FUROSEMIDE, the benzodiazepines and phenytoin are incompatible with hyaluronidase (7.1).
- Hyaluronidase should not be used to enhance the dispersion and absorption of dopamine agonist drugs (7.2).
- Local anesthetics: Hyaluronidase hastens onset and shortens duration of effect, increases incidence of systemic reactions (7.3).
- Large doses of salicylates, cortisone, ACTH, estrogens or antihistamines may require larger amounts of hyaluronidase for equivalent dispersing effect (7.4).

**ADVERSE REACTIONS**
- The most frequently reported adverse reactions have been mild local injection site reactions such as erythema, itching, and pain (6). In patients receiving large doses of salicylates, cortisone, ACTH, estrogens or antihistamines may require larger amounts of hyaluronidase for equivalent dispersing effect, since these drugs apparently render tissues partly resistant to the action of hyaluronidase.

**CONTRAINDICATIONS**
- HYLENEX recombinant may be added to small volumes of solution, such as fluid replacement solutions or solutions of drugs for subcutaneous injection. Subcutaneous fluids should be administered as directed by a physician. The dosage of subcutaneous fluids administered is dependent upon the age, weight, and clinical condition of the patient as well as laboratory determinations. The rate and volume of subcutaneous fluid administration should not exceed those employed for intravenous infusion. For premature infants or during the neonatal period, the daily dosage should not exceed 25 mL/kg of body weight and the rate of administration should not be greater than 2 mL per minute.

**Dispersion and Absorption of Injected Drugs**
- Dispersal and absorption of other injected drugs may be enhanced by adding small amounts of HYLENEX recombinant to the injection solution. It is recommended that appropriate references be consulted regarding physical or chemical incompatibilities before adding HYLENEX recombinant to a solution containing another drug.

**SUBCUTANEOUS UROGRAPHY**
- The subcutaneous route of administration of urographic contrast media is indicated when intravenous administration cannot be successfully accomplished, particularly in infants and small children. With the patient prone, 75 U of HYLENEX recombinant is injected subcutaneously over each scapula, followed by injection of the contrast medium at the same sites. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

**DOSAGE FORMS AND STRENGTHS**
- 150 USP units/mL single dose vials

**PATIENT COUNSELING INFORMATION**
- See 17 for PATIENT COUNSELING INFORMATION

**FULL PRESCRIBING INFORMATION: CONTENTS**
- 1. INDICATIONS AND USAGE
- 2. DOSAGE AND ADMINISTRATION
- 3. WARNINGS AND PRECAUTIONS
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- 15. PATIENT COUNSELING INFORMATION
- 16. HOW SUPPLIED/STORAGE AND HANDLING
- 17. PATIENT COUNSELING INFORMATION
The dosage of subcutaneous fluids administered is dependent upon the age, weight, and clinical condition. Fluids facilitated with HYLENEX recombinant.

Clinical hydration requirements for children can be achieved through administration of subcutaneous fluids. It is not known whether hyaluronidase is excreted in human milk. Because many drugs are excreted in breast milk, caution should be exercised when HYLENEX recombinant is administered to a nursing woman. It is not known whether hyaluronidase is excreted in human milk. Because many drugs are excreted in breast milk, caution should be exercised when HYLENEX recombinant is administered to a nursing woman.

8.4 Pediatric Use
Clinical hydration requirements for children can be achieved through administration of subcutaneous fluids facilitated with HYLENEX recombinant. The dosage of subcutaneous fluids administered is dependent upon the age, weight, and clinical condition. Fluids facilitated with HYLENEX recombinant.

8.5 Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

11. DESCRIPTION
HYLENEX recombinant is a purified preparation of the enzyme recombinant human hyaluronidase. HYLENEX recombinant is produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). The purified hyaluronidase glycoprotein contains 447 amino acids with an approximate molecular weight of 61,000 daltons. HYLENEX recombinant is supplied as a sterile, clear, colorless, nonpreserved, ready for use solution.

12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Hyaluronidase is a dispersion agent, which modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, a polysaccharide found in the intercellular ground substance of connective tissue, and of certain specialized tissues, such as the umbilical cord and vitreous humor. Hyaluronic acid is also present in the capsules of type A and C hemolytic streptococci. Hyaluronidase hydrolyzes hyaluronic acid by splitting the glucosaminidic bond between C1 of an N-acetylglucosamine moiety and C4 of a glucuronic acid moiety. This temporarily decreases the viscosity of the cellular cement and promotes dispersion of injected fluids or of localized transudates or exudates, thus facilitating their absorption.

Hyaluronidase cleaves glycosidic bonds of hyaluronic acid and, to a variable degree, some other mucopolysaccharides of the connective tissue. The activity is measured in vitro by monitoring the decrease in the amount of an insoluble serum albumin-hyaluronic acid complex as the enzyme cleaves the hyaluronic acid component.

12.2 Pharmacodynamics
In the absence of hyaluronidase, material injected subcutaneously disperses very slowly. Hyaluronidase facilitates dispersion, provided local interstitial pressure is adequate to furnish the necessary mechanical impulse. Such an impulse is normally initiated by injected solutions. The rate and extent of dispersion and absorption is proportionate to the amount of hyaluronidase and the volume of solution.

The reconstitution of the dermal barrier removed by intradermal injection of hyaluronidase (20, 0.2, 0.02, and 0.002 U/mL) to adult humans indicated that at 24 hours the restoration of the barrier is incomplete and inversely related to the dosage of hyaluronidase; at 48 hours, the barrier is completely restored in all treated areas. Results from an experimental study, in humans, on the influence of hyaluronidase in bone repair support the conclusion that hyaluronidase alone, in the usual clinical dosage, does not deter bone healing.

12.3 Pharmacokinetics
Knowledge of the mechanisms involved in the disappearance of injected hyaluronidase is limited. It is known, however, that the components in blood of a number of mammalian species bring about the inactivation of hyaluronidase. Studies have demonstrated that hyaluronidase is antigenic; repeated injections of relatively large amounts of hyaluronidase preparations may result in the formation of neutralizing antibodies.

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase. Hyaluronidase is found in most tissues of the body. Human studies on the effect of intravaginal hyaluronidase in sterility due to oligosperma indicated that hyaluronidase may have aided conception. Thus, it appears that hyaluronidase may not adversely affect fertility in females.

14. CLINICAL STUDIES
HYLENEX recombinant facilitated the administration of subcutaneous fluids in pediatric patients with mild to moderate dehydration in an open-label, multicenter, single arm study in fifty-one (51) patients. A subcutaneous injection of 1 ml (150 U) of HYLENEX recombinant was immediately followed by subcutaneous infusion of isotonic fluids in either the mid-anterior thigh or the inter-scapular area of the upper back.

The safety and flow rate of subcutaneously administered Lactated Ringer’s (LR) solution with and without HYLENEX recombinant was evaluated in a prospective, randomized, double-blinded, placebo-controlled, within-subject, single-center study in fifty-four (54) healthy volunteers. The mean HYLENEX recombinant facilitated infusion rate was 404 mL/hr versus 118 mL/hr for the saline control (p < 0.001, paired t-test).

15. HOW SUPPLIED/STORAGE AND HANDLING
HYLENEX recombinant is supplied sterile as 150 USP units of nonpreserved recombinant human hyaluronidase per mL in a single-use glass vial. 1 mL Single Dose Vial available in a carton of 4 (NDC 18657-102-04)

DO NOT FREEZE.

Manufactured for and Marketed by: Halozyme Therapeutics, Inc.
San Diego, CA 92121
For Product Inquiry 1-855-495-3639

Rev. August 2011  LBL293-01
3-3531-356

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U.S. Patent No. 7,767,429

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