Immune globulin subcutaneous, human – klhw (Xembify®)
Abbreviated New Drug Update (ANDU)

August 2019

OVERVIEW

• Indication
  – Treatment of primary humoral immunodeficiency (PI) in patients ≥ 2 years of age, including, but not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies

• Contraindications/Warnings
  – Contraindications — Anaphylactic or severe systemic reactions to human immunoglobulin or inactive ingredients (e.g., polysorbate 80); immune globulin A (IgA) deficient patients with anti-IgA antibodies and a history of hypersensitivity to human immune globulin treatment
  – Warnings
    • Boxed warning for thrombosis; ensure adequate hydration prior to administration and use minimum dose and infusion rate
    • Additional warnings include hypersensitivity reactions, aseptic meningitis syndrome (AMS), hemolysis and hemolytic anemia, renal dysfunction/failure, pulmonary adverse reactions (e.g., pulmonary edema/transfusion-related acute lung injury [TRALI]), transmission of infectious agents (e.g., Creutzfeldt-Jakob disease [CJD], viruses), and passive transfer of antibodies that could confound serologic testing.

• Drug Interactions
  – Passive transfer of antibodies may interfere with response to live virus vaccines including measles, mumps, rubella, and varicella.

• Common Adverse Effects
  – The most common adverse reactions (incidence ≥ 5%) reported in clinical trials with Xembify included infusion site reactions (e.g., erythema, pain, swelling, bruising, nodules, pruritus, induration, scabbing, edema), cough, and diarrhea.
• Special Populations
  – Pregnancy – No human data or animal reproduction studies have been conducted with Xembify to assess presence or absence of drug-associated risk during pregnancy. After 30 weeks gestation, immune globulins increasingly cross the placenta from maternal circulation.
  – Pediatrics – Safety and effectiveness of Xembify have not been established in patients < 2 years of age.
  – Geriatrics – Clinical trials did not include a sufficient number of patients ≥ 65 years of age to determine if their response differs from younger patients; use cautiously in this population, initiating at low doses.

• Availability
  – Solution containing 20% immune globulin G (IgG) (200 mg/mL) administration via subcutaneous (SC) infusion
  – May be self- or caregiver-administered, if deemed appropriate by healthcare provider
  – Available in 1 g (5 mL), 2 g (10 mL), 4 g (20 mL), and 10 g (50 mL) single-use vials; latex-free
  – Refrigeration required (do not freeze)

• Dosage
  – Dosing is individualized, using the patient’s pharmacokinetic and clinical response
  – Divide weekly dose by the number of administration days per week; at steady-state, doses divided and administered over a week demonstrate similar exposure as once-weekly administration; administer and document the SC infusion to the abdomen, thigh, upper arm, sides, back, and/or lateral hip (25 mL/site, ≤ 25 mL/hr/infusion site), as detailed in the Prescribing Information
  – Measure and adjust dose, if needed, 5 weeks after Xembify initiation; see Prescribing Information for details on dose adjustments and calculating difference in patient’s serum IgG and goal IgG, although clinical response should be the primary determination for dose adjustments; subsequent monitoring and adjustments, if needed, should occur every 2 to 3 months thereafter
  – When switching from an intravenous IgG (IVIG) treatment, begin Xembify 1 week after the last IVIG infusion, calculating the dose using the prior total monthly dose (in grams), dividing by the number of weeks between infusion, and multiplying by a dose adjustment factor of 1.37 (see Prescribing Information for details)
  – When switching from another SC IgG formulation, administer the same weekly dose of Xembify (in grams)

• Clinical Trials²,³
  – Study GTI1502: A multicenter, prospective, open-label, single-arm study conducted in the US and Canada compared Xembify to Gammunex-C 10% (IVIG, human) in 53 patients ≥ 2 years of age who had no serious bacterial infection (SBI) within the last 3 months prior to screening, were receiving IgG replacement infusion (IV or SC) for ≥ 3 months, and had trough levels of ≥
500 mg/dL. Following a run-in phase of 3 months (with documented achievement of steady-state), patients entered a 4 to 5 week Gammunex-C 10% IV phase, followed by a SC phase of 24 weeks with Xembify. When switching patients from Gammunex-C 10% to Xembify, a dose adjustment factor of 1.37 was used. No further dose adjustments were made. The primary efficacy endpoint for approval, which was exploratory at study design, was the rate of serious bacterial infection (SBI), defined as bacteremia/sepsis, bacterial meningitis, bacterial pneumonia, osteomyelitis/septic arthritis, or visceral abscess, during 6 months of treatment with Xembify. The SBI rate in this study was 0.05 events per subject-year (95% confidence interval [CI], 0.02 to 0.1; upper 99% confidence limit, 0.11), meeting the 1 SBI per subject-year rate threshold for efficacy. The annualized rate of infections of any kind was 2.4 (95% CI, 1.6 to 3.3) and the hospitalization rate due to infections was 0.05 (95% CI, 0.02 to 0.1). Other goals of the study were to assess bioequivalence of Xembify to Gammunex-C 10% and Xembify safety. Pharmacokinetic data attained from 41 patients demonstrated bioequivalence of the 2 agents. Safety data was attained from 49 patients (4 subjects withdrew during run-in phase), including 14 patients ages 2 to 16 years, who received 1,053 infusions at a median dose of 171 mg/kg/week (range, 71 mg/kg/week to 276 mg/kg/week) for a total exposure of 20.28 subject-years. No deaths, thromboembolic events, anaphylaxis, or other serious adverse events occurred during the study.

- An interim safety analysis of a non-US trial in 32 adults and 29 children demonstrated similar results; however, the trial is ongoing and may provide additional safety and efficacy data in children.

**CLINICAL CONSIDERATIONS**

- The American Academy of Allergy, Asthma, & Immunology (AAAAI) Primary Practice parameter and evidence review for the diagnosis and treatment of PI recommends antimicrobials, IgG replacement, and more invasive procedures (e.g., stem cell and/or lung transplant) for particular disease complications. The recommendation does not favor a particular IgG replacement.
- For IgG replacement, AAAAI recommends checking IgG trough levels after fifth infusion, after infection, when clinical response not achieved, and periodically if the patient is self-administering the product. AAAAI recommends that trough levels should remain above 500 mg/dL, and above 800 mg/dL if hypogammaglobulinemic.
- AAAAI recommends SC IgG as a valuable alternative to IVIG, noting the potential for treating CIDP and other muscle and nerve disorders. There are several SC IgG replacement treatment options currently on market. Like other 20% protein solutions available, Xembify requires patients to infuse less drug at a slower rate to limit adverse events, compared to IVIG and lower strength SC IgG formulations.
- Xembify, approved on July 3, 2019, is a weekly self-administered SC infusion for patients with PI. Grifols’ Xembify is expected to be available in the last quarter of 2019.
# Suggested Utilization Management

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<thead>
<tr>
<th>Anticipated Therapeutic Class Review (TCR) Placement</th>
<th>Immune Globulins</th>
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<tbody>
<tr>
<td>Clinical Edit</td>
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## Initial Approval Criteria

Patient must:

- Be ≥ 2 years old; **AND**
- Have diagnosis of primary humoral immunodeficiency (PI) (e.g., congenital agammaglobulinemia, common variable immunodeficiency, X linked agammaglobulinemia, Wiskott Aldrich syndrome, and severe combined immunodeficiencies); **AND**
- Baseline values for blood urea nitrogen (BUN) and serum creatinine obtained within 30 days of request; **AND**
- Patient’s immunoglobulin G (IgG) level is < 200 mg/dL; **OR**
- Patient meets both of the following criteria:
  - Patient has a history of multiple hard to treat infections as indicated by ≥ 1 of the following:
    - Four or more ear infections within 1 year; **OR**
    - Two or more serious sinus infections within 1 year; **OR**
    - Two or more months of antibiotics with little effect; **OR**
    - Two or more pneumonias within 1 year; **OR**
    - Recurrent or deep skin abscesses; **OR**
    - Need for intravenous antibiotics to clear infections; **OR**
    - Two or more deep-seated infections including septicemia; **AND**
  - The patient has a deficiency in producing antibodies in response to vaccination; **AND**
    - Titers were drawn before challenging with vaccination; **AND**
    - Titers were drawn between 4 and 8 weeks of vaccination.
Suggested Utilization Management (continued)

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<thead>
<tr>
<th>Clinical Edit (continued)</th>
<th>Renewal Criteria</th>
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<td>Patient must:</td>
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<td>• Continue to meet criteria identified above; AND</td>
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<td>• Not have unacceptable toxicity from the drug (e.g., severe hypersensitivity/anaphylaxis, thrombosis, aseptic meningitis syndrome, hemolytic anemia, hyperproteinemia, acute lung injury); AND</td>
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<td>• BUN and serum creatinine obtained within the last 6 months and the concentration and rate of infusion have been adjusted accordingly; AND</td>
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<td>• Disease response as evidenced by ≥ 1 of the following:</td>
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<td>- Decrease in the frequency of infection; OR</td>
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<tr>
<td>- Decrease in the severity of infection</td>
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<th>Quantity Limit</th>
<th>24 g/week; 96 g/28 days</th>
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<tr>
<th>Duration of Approval</th>
<th>Initial: 6 months</th>
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<tr>
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<td>Renewal: 1 year</td>
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<th>Drug to Disease Hard Edit</th>
<th>None</th>
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REFERENCES