PHARMACY & THERAPEUTICS COMMITTEE PRODUCT EVALUATION

Rep:

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GENERIC NAME: loncastuximab tesirine-lpyl

PROPRIETORY NAME: Zynlonta®

INDICATION:

- On April 23, 2021, the Food and Drug Administration granted accelerated approval to loncastuximab tesirine-lpyl (Zynlonta, ADC Therapeutics SA), a CD19-directed antibody and alkylating agent conjugate, for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

MECHANISM OF ACTION:

- Loncastuximab tesirine-lpyl is a CD19-directed antibody and alkylating agent conjugate. Upon binding to CD19, loncastuximab tesirine-lpyl is internalized followed by release of SG3199 via proteolytic cleavage. The released SG3199 binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks, subsequently inducing cell death

PHARMACOKINETICS

Metabolism

- (Loncastuximab) Metabolized into small peptides by catabolic pathways
- (SG3199) Substrate of CYP3A4/5 and P-gp

Excretion

- Renal excretion: Minimal (SG3199)
- Total body clearance: 0.275 L/day (steady-state)

Elimination Half Life

- 20.8 days

BLACK BOX WARNING: None

Warning/PRECAUTIONS

- Cardiovascular: Serious effusion and edema, including pericardial effusion, peripheral edema, and ascites, have been reported; monitoring is recommended and interruption of therapy and treatment may be necessary. Consider diagnostic imaging in symptomatic patients
- Dermatologic: Serious cutaneous adverse reactions, including photosensitivity reactions, rash (ie, exfoliative and maculo-papular), and erythema, have been reported; monitoring is recommended and interruption of therapy and dermatology consultation may be necessary. Minimize or avoid exposure to direct natural or artificial sunlight, including exposure through glass windows and use skin protection (eg, sun-protective clothing and/or sunscreen)
- Hematologic: Serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia, and febrile neutropenia have been reported; monitoring is recommended and interruption of therapy, dose reduction, or discontinuation may be necessary. Consider prophylactic administration of granulocyte colony-stimulating factor

- Immunologic: Fatal and serious infections, including opportunistic infections, have been reported; monitoring is recommended and interruption of therapy may be necessary .
- Reproductive: May cause fetal harm; advise females of reproductive potential to use effective contraception during therapy and for 9 months after the last dose and male patients with female partners of reproductive potential to use effective contraception during treatment and for 6 months after the last dose
- Respiratory: Serious effusion, including pleural effusion, has been reported; monitoring is recommended and interruption of therapy and treatment may be necessary. Consider diagnostic imaging in symptomatic patients

ADVERSE REACTIONS

- **Common**
- **Gastrointestinal:** Nausea (23%)
- **Hematologic:** Decreased hemoglobin, All Grades (51%), Decreased neutrophil count, All Grades (52%), Decreased platelet count (58%)
- **Musculoskeletal:** Musculoskeletal pain (23%)
- **Other:** Fatigue (38%)
- **Serious**
- **Cardiovascular:** Edema (28%), Pericardial effusion (3%)
- **Dermatologic:** Erythema, Photosensitivity (10%), Rash (30%)
- **Hematologic:** Anemia, Grade 3 or 4 (12%), Febrile neutropenia (3%), Neutropenia, Grade 3 or 4 (32%), Thrombocytopenia, Grade 3 or 4 (20%)
- **Respiratory:** Pleural effusion (10%)
- **Other:** Infectious disease

DRUG INTERACTIONS:

- **N/A**

RECOMMENDED DOSE AND SCHEDULE

- The recommended loncastuximab tesirine-lpyl dosage is 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles, by intravenous infusion over 30 minutes on day 1 of each cycle (every 3 weeks).
- For patients with a body mass index (BMI) ≥35 kg/m2 , calculate the dose based on an adjusted body weight (ABW) as follows: ABW in kg = 35 kg/m2 × (height in meters)2
- Patients should be premedicated with dexamethasone 4 mg orally or intravenously twice daily for 3 days beginning the day before loncastuximab tesirine-lpy

DOSAGE ADJUSTMENTS

- Renal impairment: No specific recommendations are available

- Hepatic impairment (mild, total bilirubin ULN or less and AST greater than ULN or total bilirubin greater than 1 to 1.5x ULN and any AST): No dose adjustment is recommended; monitor for increased incidence of adverse reactions and modify the dosage in the event of adverse reactions
- Hepatic impairment (moderate or severe, total bilirubin greater than 1.5x ULN and any AST): No specific recommendations are available; has not been studied in this population
- Geriatrics: No specific recommendations are available; no overall differences in safety or effectiveness were observed between these patients and younger patients
- Edema or effusion (Grade 2 or higher): Withhold therapy until the toxicity resolves to Grade 1 or less; if dosing is delayed by more than 3 weeks due to toxicity, reduce subsequent doses by 50%; if toxicity requires dose reduction following the second dose of 0.15 mg/kg (cycle 2) give a dose of 0.075 mg/kg for cycle 3; if toxicity reoccurs following dose reduction, consider discontinuation
- Neutropenia (absolute neutrophil count less than 1 x 10(9)/L): Withhold therapy until neutrophil count returns to 1 x 10(9)/L or higher; if dosing is delayed by more than 3 weeks due to toxicity, reduce subsequent doses by 50%; if toxicity requires dose reduction following the second dose of 0.15 mg/kg (cycle 2) give a dose of 0.075 mg/kg for cycle 3; if toxicity reoccurs following dose reduction, consider discontinuation
- Other nonhematologic adverse reaction (Grade 3 or higher): Withhold therapy until the toxicity resolves to Grade 1 or less; if dosing is delayed by more than 3 weeks due to toxicity, reduce subsequent doses by 50%; if toxicity requires dose reduction following the second dose of 0.15 mg/kg (cycle 2) give a dose of 0.075 mg/kg for cycle 3; if toxicity reoccurs following dose reduction, consider discontinuation
- Thrombocytopenia (platelet count less than 50,000/mcL): Withhold therapy until platelet count returns to 50,000/mcL or higher; if dosing is delayed by more than 3 weeks due to toxicity, reduce subsequent doses by 50%; if toxicity requires dose reduction following the second dose of 0.15 mg/kg (cycle 2) give a dose of 0.075 mg/kg for cycle 3; if toxicity reoccurs following dose reduction, consider discontinuation

PRODUCT AVAILABILITY & NDCs:

- How Supplied ZYNLONTA (loncastuximab tesirine-lpyl) for injection is a sterile, preservative-free, white to off-white lyophilized powder, which has a cake-like appearance, supplied in a single-dose vial for reconstitution and further dilution. Each carton (NDC 79952-110-01) contains one 10 mg single-dose vial.
- Storage and Handling Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not use beyond the expiration date shown on the carton. Do not freeze. Do not shake.
- Special Handling ZYNLONTA is a hazardous drug. Follow applicable special handling and disposal procedures. Any unused drug product or waste material should be disposed in accordance with local requirements.

CLINICAL LITRATURE

Approval was based on LOTIS-2 (NCT03589469), an open-label, single-arm trial in 145 adult patients with relapsed or refractory DLBCL or high-grade B-cell lymphoma after at least two prior systemic regimens. Patients received loncastuximab tesirine-lpyl 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles. Patients received treatment until progressive disease or unacceptable toxicity.

The main efficacy outcome measure was overall response rate (ORR), as assessed by an independent review committee using Lugano 2014 criteria. The ORR was 48.3% (95% CI: 39.9, 56.7) with a complete response rate of 24.1% (95% CI: 17.4, 31.9). After a median follow-up of 7.3 months, median response duration was 10.3 months (95% CI: 6.9, NE). Of the 70 patients who achieved objective responses, 36% were censored for response duration prior to 3 months.

REFERENCES:

- Product Information: ZYNLONTA(TM) intravenous injection, loncastuximab tesirine-lpyl intravenous injection. ADC Therapeutics America (per FDA), Murray Hill, NJ, 2021.