PRESCRIBING INFORMATION

Qartemi® (varnimcabtagene autoleucel)
Suspension for intravenous infusion

To be provided on the prescription of a cancer specialist / oncologist for the treatment of relapsed / refractory B-NHL patients aged greater than 18 years of age.

1. Generic Name

Varnimcabtagene autoleucel

2. Qualitative and quantitative composition

One dose of **Qartemi®** contains 0.1 x 10^6 to 5 x 10^6 anti-CD19 CAR-positive T cells/Kg in approximately 30 mL suspension containing 10% (v/v) of DMSO, 40% (v/v) of 20% HSA and 50% (v/v) of 0.9% Sodium Chloride solution.

3. Dosage form and strength

Qartemi® is intended for autologous and intravenous use only.
One dose of **Qartemi®** contains 0.1 x 10^6 to 5 x 10^6 CAR-positive viable T cells per kg of body weight and is dispensed in three fractions – 10%, 30%, 60%, divided into three infusion bags of approximately 30 mL each.

4. Clinical particulars

4.1 Therapeutic indication

Qartemi® is an anti-CD19 directed genetically modified autologous Chimeric Antigen Receptor T (CAR-T) cell immunotherapy indicated for the treatment of patients with Relapsed / Refractory B Cell Non-Hodgkin Lymphoma (B-NHL) in patients aged greater than 18 years of age.

4.2 Posology and method of administration

For autologous use only. For intravenous use only**.**

4.3 Contraindications

None.

4.4 Special warnings and precautions for use

- **Qartemi®** is for autologous use only. The patient's identity must match the patient identifiers on the **Qartemi®** infusion bag(s). Do not infuse **Qartemi®** if the information on the patient-specific label(s) does not match the intended patient.
- **Qartemi®** dose is contained in three patient-specific infusion bag(s). Verify the number of bags received and ensure **Qartemi®** is stored at the recommended temperature onsite till all bags have been infused.
- Cytokine Release Syndrome (CRS), including fatal or life-threatening reaction, may occur in patients following treatment with **Qartemi®**.
- Do not administer to patients with active infection or inflammatory disorders.
- Neurologic toxicities may occur following treatment with **Qartemi®**, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with **Qartemi®**.
- Prolonged cytopenia with bleeding and infection may occur following treatment with **Qartemi®**.
- Allergic reactions may occur with the infusion of **Qartemi®**. Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) in **Qartemi®**.
- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD19 CAR-T cell therapy. Perform screening for HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) in accordance with clinical guidelines before collection of cells for manufacturing.
- Hypogammaglobulinemia can occur in patients receiving treatment with **Qartemi®**. Monitor immunoglobulin levels after treatment with **Qartemi®**.
- Safety of immunization with live viral vaccines during or following **Qartemi®** treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepletion preparative regimen, during **Qartemi®** treatment, and until immune recovery following treatment with **Qartemi®**.
- Due to the potential for neurologic events, including altered mental status or seizures, patients receiving **Qartemi®** may be at risk for altered or decreased consciousness or coordination in the 8 weeks following **Qartemi®** infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.
- Ensure that a minimum of 4 doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Central venous access may be utilized for the infusion of **Qartemi®** and is encouraged in patients with poor peripheral access.

- Secondary malignancies may occur following treatment with **Qartemi®**.

4.5 Drugs interactions

There are no known interactions with other drugs.

Laboratory Test Interactions: HIV and the lentivirus used to make **Qartemi®** have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests may yield false-positive results in patients who have received **Qartemi®**.

4.6 Use in special populations

- There are no available data with **Qartemi®** use in pregnant and lactating women.
- **Qartemi®** is not currently approved for paediatric use.
- Safety and efficacy of **Qartemi®** in patients older than 80 years has not been established yet.

4.7 Effects on ability to drive and use machines

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving **Qartemi®** may be at risk for altered or decreased consciousness or coordination in the 8 weeks following **Qartemi®** infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

4.8 Undesirable effects

The following undesirable effects are reported:

- Cytokine Release Syndrome
- Neurologic Toxicities
- Hypersensitivity Reactions
- Infections
- Cytopenias
- Hypogammaglobulinemia

Also, other adverse events which occurred in at least 10% of patients treated with **Qartemi®** include:

- **Blood and lymphatic system disorders:** B-cell aplasia, Lymphopenia, Neutropenia, Anaemia, Thrombocytopenia, Leukopenia, Febrile neutropenia, Coagulopathy
- **Cardiac disorders:** Sinus tachycardia, Sinus bradycardia
- **Ear and labyrinth disorders:** Vertigo
- **Eye disorders:** Eyelid Oedema, Keratitis, Lacrimation increased, Photophobia, Refraction disorder, Visual impairment.
- **Gastrointestinal disorders:** Vomiting, Nausea, Stomatitis, Diarrhoea, Abdominal pain, Constipation, Odynophagia, Toothache, Abdominal discomfort, Abdominal pain, Abnormal faeces, Anal fissure, Melaena, Haemorrhage, Rectal haemorrhage, Haemorrhoid infection
- **General disorders and administration site conditions:** Pyrexia, Fatigue, Asthenia, Infusion related reaction, Chills, Mucositis Inflammation, Oedema, Pain, Infusion site eczema
- **Hepatobiliary disorders:** Cholestasis, Venoocclusive liver disease, Biliary fistula, Hyperbilirubinaemia
- **Immune system disorders:** Cytokine release syndrome, Hypogammaglobulinaemia
- **Infections and infestations:** Bacterial, Viral and Fungal infections including Upper respiratory tract infection, COVID-19, Vascular device infection.
- **Investigations:** C-reactive protein increased, Serum ferritin increased, Blood magnesium decreased, Interleukin level increased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased
- **Metabolism and nutrition disorders:** Hypocalcaemia, Hypokalaemia, Decreased appetite, Acidosis, Hyperglycaemia, Hypoalbuminemia, Hyponatremia, Hypomagnesaemia
- **Musculoskeletal and connective tissue disorders:** Arthralgia, Bone pain, Back pain, Myalgia, Musculoskeletal pain
- **Nervous system disorders:** Headache, Dysgeusia, Dizziness, Meningitis, Neurotoxicity, Tremors, Ischaemic cerebral infarction, Facial paralysis, Hyperesthesia, Paraesthesia, Seizure, Syncope
- **Psychiatric disorders:** Anxiety
- **Renal and urinary disorders:** Renal failure
- **Reproductive system and breast disorders:** Gynaecomastia
- **Respiratory, thoracic and mediastinal disorders:** Cough, Epistaxis, Pleural effusion, Acute pulmonary oedema, Bronchospasm, Oropharyngeal pain, Nasal congestion, Pneumonitis, Rhinitis allergic, Tachypnea
- **Skin and subcutaneous tissue disorders:** Erythema including Facial erythema, erythema in extremities and erythematous rash, Eczema, Ecchymosis, Petechiae
- **Vascular disorders:** Hypertension, Hypotension, Air embolism, Orthostatic hypotension, Retinal haemorrhage, Secondary hypertension

4.9 Overdose
Not applicable, as **Qartemi®** is administered in a hospital setting under constant clinical supervision.

5. Pharmacological properties

5.1 Mechanism of Action
Qartemi® is a chimeric antigen receptor (CAR)-positive T cell therapy targeting CD19, which is expressed on the surface of normal and malignant B cells. The CAR construct includes an anti-CD19 single-chain variable fragment (scFv)-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T cell activation domain, and a 4-1BB costimulatory domain. Antigen-specific activation of **Qartemi®** results in CAR-positive T cell proliferation, cytokine secretion, and subsequent cytolytic killing of CD19-expressing cells.

5.2 Pharmacodynamic properties
Following **Qartemi®** infusion, pharmacodynamic responses of CAR activation and anti-tumor efficacy were evaluated. Peak elevation of cytokines occurred within 14 days of infusion. Rapid decrease in tumor markers associated with clinical response have been observed within the first month following infusion. Due to the on-target effect of **Qartemi®** B cell aplasia would be expected.

5.3 Pharmacokinetic properties
Distribution: CAR-T cells migrate in physiological conditions to peripheral tissues where the target antigen is located. In a similar way as the natural T cells, the CAR-T cells are widely distributed in blood and tissues. There is no additional information on the distribution profile of **Qartemi®**.
Metabolism and elimination: **Qartemi®** is made of human autologous T-cells. The metabolic products expected to be obtained are typical cell degradation products resulting from normal mechanisms of cell elimination. T cells have a proliferative capacity with a lifespan of several years. Therefore, their persistence in the human body once they are infused is limited to that period. They will be later eliminated from the body by normal physiologic processes.

6. Nonclinical properties
6.1 Animal Toxicology or Pharmacology
There are no in vitro representative assays or ex vivo or in vivo models reflecting with precision the toxicological properties of **Qartemi®**.
There were no genotoxicity or carcinogenic studies conducted with **Qartemi®**.

No studies were conducted to evaluate the effects of **Qartemi®** on fertility, reproduction, and development.

7. Description
Qartemi® (autologous anti-CD19-transduced CD3+ cells) is a cell and gene therapy medicinal product containing autologous T cells genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv; A3B1 binder) linked to 4-1BB co-stimulatory domain and CD3-zeta signalling domain.

Binding of **Qartemi®** to CD19-expressing target cells leads to CAR-positive T cell activation. Antigen-specific activation of **Qartemi®** results in CAR-positive T cell proliferation, cytokine secretion, and subsequent cytolytic killing of CD19-expressing cells.

Qartemi® is prepared from the patient's peripheral blood mononuclear cells (PBMCs), which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells by CD4 and CD8 selection, through activation with anti-CD3 and anti-CD28 antibodies in the presence of IL-7 and IL-15, which are then transduced with the replication-incompetent lentiviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in three patient-specific infusion bags. The product is thawed prior to infusion back into the patient. **Qartemi®** formulation contains DMSO concentration of 10% in the final product.

Access to **Qartemi®** will be available only through a qualified healthcare facility.

8. Pharmaceutical particulars
8.1 Incompatibilities
Qartemi® is a personalized product intended for autologous and intravenous use only.

8.2 Shelf-life
Twelve months from the date of manufacturing when stored at temperature ≤ -150°C in vapor phase of liquid nitrogen.

8.3 Packaging information

Qartemi® is supplied in three infusion bags individually packed in an aluminium cassette stored at temperature ≤ -150°C in vapor phase of liquid nitrogen with patient-specific labels.

8.4 Storage and handing instructions

Qartemi® is supplied in three infusion bags:

- Bag-1: 30 mL infusion bag and aluminium cassette (10% of total dose)
- Bag-2: 30 mL infusion bag and aluminium cassette (30% of total dose)
- Bag-3: 30 mL infusion bag and aluminium cassette (60% of total dose)

- Match the identity of the patient with the patient identifiers on the cassette(s) and infusion bag(s) upon receipt.
- Inspect the infusion bag(s) for any breaches of container integrity such as breaks or cracks before thawing. If the bag(s) is compromised, contact the manufacturer immediately.
- Administer a lymphodepletion preparative regimen of cyclophosphamide and fludarabine over 3 days before infusion of **Qartemi®**.
- Administer **Qartemi®** 2 days after completion of lymphodepletion preparative regimen.
- Confirm the patient's identity prior to thawing and infusion.
- Premedicate with paracetamol and diphenhydramine at least 30 minutes prior to infusion.
- Avoid prophylactic use of dexamethasone or other systemic corticosteroids.
- Confirm availability of tocilizumab prior to infusion.
- Thaw **Qartemi®** infusion bag(s) at approximately 37°C using a water bath or dry thawer until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or resuspend **Qartemi®** in new media prior to infusion.
- **Qartemi®** should be administered within 60 minutes of the start of thaw.
- Use a regular IV infusion set for administration of **Qartemi®**. Do NOT use a leucodepletion filter.
- Do NOT irradiate / manipulate **Qartemi®**.
- All three **Qartemi®** infusion bags should be administered within 10 days from first infusion.

9. Patient Counselling Information

Ensure that patients understand the risk of manufacturing failure. In case of a manufacturing failure, a second manufacturing of **Qartemi®** may be attempted. In addition, while the patient awaits the product, other anticancer treatment (not lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period, which could delay or prevent the administration of **Qartemi®**.

Advise patients to seek immediate attention for any of the following:

- **Cytokine Release Syndrome (CRS):** Signs or symptoms associated with CRS, including fever, hypotension, tachycardia, chills, hypoxia, headache, and fatigue.
- **Neurologic Toxicities / Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS):** Signs or symptoms associated with neurologic events, including encephalopathy, confusion, seizures, tremor, aphasia, delirium, and somnolence.
- **Infections:** Signs or symptoms associated with infections.
- **Prolonged Cytopenias:** Signs or symptoms associated with bone marrow suppression, including neutropenia, anemia, thrombocytopenia, or febrile neutropenia.

Advise patients for the need to:

- Have periodic monitoring of blood counts before and after **Qartemi®** infusion.
- Refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after **Qartemi®** administration.

10. Details of manufacturer

Immuneel Therapeutics Private Limited, 29/P2, 8th Floor, Narayana Health City, Hosur Road, Bommasandra Industrial Area, Bengaluru, Karnataka, India, 560099.

11. Details of permission or licence number with date

Lic. No.: KTK/28/0474/2024, Date: 07 May 2024

12. Date of revision: 15 July 2024

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