HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NexCAR19 safely and effectively. See full prescribing information for NexCAR19.

NexCAR19™ (Actalycabtagene autoleucel) suspension for intravenous infusion

Generic Name: Autologous HCAR19 (2nd generation Anti-CD19-41BBCD3ζ chimeric antigen receptor T-cell therapy)

Nonproprietary Names (INN): Actalycabtagene autoleucel (Actaly-cel)
Initial CDSCO approval: 2023
CDSCO permission number: MF-01/2023

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES
See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, can occur in patients receiving NexCAR19. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids (6.1).**
- **No Neurologic toxicities, including fatal or life-threatening reactions occurred in patients receiving NexCAR19, including concurrently with CRS or after CRS resolution. Patients however, must be monitored closely for symptoms that indicate onset of neurologic toxicities after treatment with NexCAR19. Provide supportive care and/or corticosteroids as needed (6.2).**
- **Patient with active neurological autoimmune or inflammatory disorder should be given NexCAR19 at physician's discretion.**

----------INDICATIONS AND USAGE----------
NexCAR19 is a 2nd generation Anti-CD19-4-1BB-CD3ζ chimeric antigen receptor T-cell therapy indicated for the treatment of patients (Age ≥ 15 years) diagnosed with -

- Relapsed/ Refractory B Cell Lymphomas (1.1)
- Relapsed/ Refractory B- Acute Lymphoblastic Leukemia (1.1).

Limitations of Use:

- NexCAR19 is not indicated for the treatment of patients with primary central nervous system lymphoma.
- NexCAR19 is not indicated for the treatment of patients with active CNS involvement by malignancy. Patients with a history of CNS disease that has been treated effectively will be eligible.
- NexCAR19 is not recommended for pregnant or lactating women. Pregnancy after treatment with NexCAR19 Infusion must be discussed with the treating physician.

----------DOSAGE AND ADMINISTRATION----------
For autologous use only. For intravenous use only.

- Do NOT use a leukoreduction filter (2.2).
- Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of NexCAR19 (2.2).
- Confirm Patient ID prior to infusion and verify Patient ID in a conspicuous manner (2.2).
- Premedicate with acetaminophen and antihistamine prior to infusion (2.2).
- Confirm availability of tocilizumab and anakinra prior to infusion (2.2).
- The NexCAR19 dose: ≥ 5 million CAR-T cells/ kg upto 2 x 10^9 viable CAR-T cells in a single infusion (2.1).

----------DOSAGE FORMS AND STRENGTHS----------

- NexCAR19 is available as a cell suspension for infusion (4).
- Dosage Form: Cryopreserved viable CAR-T cells in infusion bag for single dose intravenous infusion (autologous) in 100 ml (4)
- Composition: Each 100ml of cryopreserved cell suspension contains – 1 x 10^8 – 2 x 10^9 anti-CD 19 CAR-T cells, 5% Dimethyl sulfoxide (DMSO), 6% pentastarch, 3.4% human serum albumin (HSA) and 1000 IU Heparin in Plasma-Lyte A solution q.s (4)
- Dose: ≥ 5 million CAR-T cells/ kg up to 2 x 10^9 viable CAR-T cells in a single infusion (4).

----------CONTRAINDICATIONS----------

- None (5).

----------WARNINGS AND PRECAUTIONS----------

- Aseptic Conditions: Proper Aseptic conditions should be followed while thawing and handling the product (14.2).
- ICU support should be available at the clinical site where infusion is given (2.2).
- Patients with active neurological autoimmune or inflammatory disorder should be given NexCAR19 at physician's discretion (6.2).
- Serious Infections: Monitor patients for signs and symptoms of infection; treat appropriately (6.4).
- Prolonged Cytopenia: Patients may exhibit Grade 3 or higher cytopenia for several weeks following NexCAR19 infusion. Monitor complete blood counts and manage as per institutional guidelines (6.5).
- Hypogammaglobulinemia: Monitor and provide replacement therapy (6.6).
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving NexCAR19 (6.9).

----------ADVERSE REACTIONS----------
The most common adverse reactions excluding laboratory abnormalities, in patients with R/R B-Cell Malignancies are Cytokine Release Syndrome, Hypogammaglobulinemia, Febrile reactions, nausea, fatigue, Hemophagocytic lymphohistiocytosis (HLH) and hypotension (7).
The most common Grade 3-4 laboratory abnormalities are neutropenia, anemia, thrombocytopenia, leukopenia and lymphopenia (7).

See PATIENT COUNSELING INFORMATION and Medication Guide for more information (15).

Table of Contents

FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- **Cytokine Release Syndrome (CRS), occurred in patients receiving NexCAR19. Do not administer NexCAR19 to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids *[see Management of Serious Adverse Reactions (3), Warnings and Precautions (6.1,6.2,6.3,6.4,6.5,6.6,6.7,6.8,6.9)]*.**
- **Neurologic toxicities were not observed in patients receiving NexCAR19. Monitor for neurologic toxicities after treatment with NexCAR19. Provide supportive care and/or corticosteroids as needed *[see Management of Serious Adverse Reactions (3), Warnings and Precautions (6.2)]*.**

1. INDICATIONS

1.1 Indications for NexCAR19:

NexCAR19 is a 2nd generation Anti-CD19-4-1BB-CD3ζ chimeric antigen receptor T-cell therapy indicated for the treatment of patients (Age ≥ 15 years) diagnosed with -

- Relapsed/ Refractory B Cell Lymphomas
- Relapsed/ Refractory B- Acute Lymphoblastic Leukemia

2. DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

2.1. Dosage form

Cryopreserved viable CAR-T cells in an infusion bag for single dose intravenous infusion (autologous) in 100 ml.

Composition: Each 100ml of cryopreserved cell suspension contains –

$1 \times 10^8 – 2 \times 10^9$ anti-CD 19 CAR-T cells, 5% Dimethyl sulfoxide (DMSO), 6% pentastarch, 3.4% human serum albumin (HSA) and 1000 IU Heparin in Plasma-Lyte A solution q.s

Dose: ≥ 5 million CAR-T cells/ kg up to 2×10^9 viable CAR-T cells in a single infusion.

2.2. Administration

NexCAR19 is for autologous use only. The patient's identity must match the patient identifiers on the NexCAR19 aluminum cassette and infusion bag. Confirm patient ID prior to infusion and verify patient ID in a conspicuous manner. Do not infuse NexCAR19 if the information on the label does not match the intended patient.

Preparing Patient for NexCAR19 Infusion

Confirm availability of NexCAR19 prior to starting the lymphodepleting regimen.

Treatment regimen:

2.2.1 Lymphodepleting chemotherapy:

A lymphodepleting chemotherapy has to be administered prior to the infusion of NexCAR19. The following regimen is recommended to be used over three days:

Fludarabine 30 mg/m^2 and Cyclophosphamide 500 mg/m^2 for three days. Infusion is recommended to be given 2-7 days after lymphodepleting chemotherapy.

2.2.2 Infusion of NexCAR19:

Dose: ≥ 5 million CAR-T cells/ kg up to 2×10^9 viable CAR-T cells in a single infusion.

Route of Administration: Single Dose Intravenous Infusion.

2.2.3 Preparation of NexCAR19 for Infusion

- Delay the infusion of NexCAR19 if a patient has unresolved serious adverse reactions (including pulmonary reactions, cardiac reactions, or hypotension) from preceding chemotherapies, active uncontrolled infection, active graft versus host disease (GVHD), or worsening of leukemia burden following lymphodepleting chemotherapy.
- Verify the number of bag(s)s received for the dose of NexCAR19 with the Certificate of Conformance (CoC) and Certificate of Analysis (CoA).
- The product should not be infused if there is any visible damage or leakage in the bag(s). Inspect the bag(s) for the same. In case of any damage or leakage, do not infuse the patient; contact ImmunoACT.
- Thawing process: The product should be gently thawed in a water bath at 36 to 38°C. There should be no frozen clumps in the bag(s). The time between product thawing and completion of the infusion should not exceed 30 minutes to maintain maximum product viability. NexCAR19 must not be thawed until the subject is ready for the infusion.
- Pre-medication: Premedicate the patient with Inj. Avil 1 amp + Tab. Paracetamol 15mg/kg approximately 20 – 30 minutes prior to the infusion. Prior to NexCAR19 infusion preparation, confirm the patient's identity with patient identifiers mentioned on the infusion bag(s). Confirm patient ID prior to infusion and verify patient Id in a conspicuous manner.

Monitoring

- Monitor patients following infusion for signs and symptoms of CRS and neurologic toxicities.
- ICU support should be available at the clinical site where infusion is given.
- Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.2.4 Incompatibilities

Following are list of medications or therapies that are recommended to be kept on hold prior to apheresis and/or infusion:

- Steroids must be stopped at least 24 hrs prior to apheresis and infusion.
- Immunosuppressive medications and anti-proliferating therapies must be stopped at least 1 week prior to apheresis and infusion.
- Short acting drugs like TKIs and hydroxyurea must be stopped at least 24 hrs prior to apheresis and infusion.
- Cytotoxic drugs including low dose daily or weekly maintenance therapies must be stopped 1 week prior to apheresis and infusion
- Antibodies including anti CD-20 therapy must be stopped within 4 weeks before infusion or 5 half-lives respectively whichever is longer.
- CNS disease prophylaxis must be stopped at least 1 week before infusion.
- Radiation therapy should be stopped at least 1 week before infusion.
- For leukemia patients, a time gap of at least 28 days must be maintained between donor lymphocyte infusions and Autologous HCAR19 infusions.
- The patient who is post allogeneic stem-cell transplant should be off-immunosuppression for at least 2 weeks.

3. Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to ASTCT guidelines (Table 1).

Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life- threatening CRS, consider intensive-care supportive therapy.

Table 1. CRS Management Guidance

Sr. No.	Check	Action
1	Fever	Initiate Febrile Neutropenia management Cardiac/SPO2 monitoring Move to next step
2	Blood pressure and SPO2 Normal	Symptomatic treatment Tocilizumab-1 dose if fever >3 days
3	Hypotension and/or Hypoxia	IVF 1-2-unit NS, repeat once Supplemental oxygen, if needed. Tocilizumab[1] and Dexamethosone 4-10 mg IV-1 dose
4	Hypotension persists after IV fluids Oxygen requirement > 6l/min	2 D Echo, Cardiac markers Start Vasopressors Shift to ICU Tocilizumab[1] Dexamethasone -10mg-20mg[2] q6h Check Coagulopathy chart
5	Hypotension persists- > 1 Vasopressor (Exclude Vasopressin) OR Norepinephrine equivalent[3] > 15 mcg/min Positive pressure required-NIV or mechanical ventilation	Tocilizumab[1] Methylprednisolone 1g/day- 3 days Refractory >24hrs or worsening rapidly- Additional therapies[4] Check coagulopathy chart

[1] Tocilizumab- 8mg/kg IV (Max dose-800mg), repeat upto 3 doses in 24 hrs, Maximum-4 doses for the entire course of CRS.

[2] Dexamethasone- **10mg**- 1 vasopressor, **20mg**- 2 vasopressors/No improvement in hypoxia within 24 hours/progression of lung infiltrates/increase in FiO^2

[3] Norepinephrine equivalent dose = [norepinephrine (mcg/minute)] + [dopamine (mcg/kg/minute) / 2] + [epinephrine (mcg/minute)] + [phenylephrine (mcg/minute) / 10]

[4] Additional therapies-

1. Anakinra- 100 mg SC daily for 7 days (Avoid if Cr Clearance <30)
2. Cyclophosphamide- 1.5 g/m^2 One dose (With Mesna 1.5g/m^2 over 24 hours)
3. ATG- 1-2 mg/kg/d for D1-3, Premed with steroid and pheniramine, Infuse over 6h.

References: - 1. MDACC CARTOX guidelines 2018. 2. ASTCT classification BBMT 3. How I manage CAR-T toxicities Reagan P, JCO 2021.

Neurological Toxicity

Monitor patients for signs and symptoms of neurological toxicity/immune effector cell-associated neurotoxicity syndrome (ICANS) (Table 2). Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities.

Table 2. Neurological Toxicity/ICANS Grading and Management Guidance
ICANS is defined by the presence of these symptoms in < 8 weeks from CAR-T infusion.
(IC bleed/tremors/myoclonus are not considered)

Sr. No.	Check	Action
1	IEC score[1] 7-9 AND Wakes spontaneously	Evaluate for ICANS[2] Supportive care[3] (For all patients) Dexamethasone 10 mg IV 1 dose and reassess in 6 hours
2	IEC score 3-6 OR Awakes to verbal stimulus	Dexamethasone 10 mg IV q 12 hrs Taper and stop once improvement
3	IEC score 0-2 OR Awakes to tactile stimulus OR Any clinical seizure that resolves in <5min OR Non-convulsive seizure that responds to intervention Focal edema on imaging	Shift to ICU Airway protection If brain edema- Maintain MAP within 20-25 mm Hg of baseline MAP Correct coagulopathy and uremia Seizure management[4] Monitor for ICT Dexamethasone 10mg q6h, increase to 20mg q6h if Grade 3 persists 24h Methylprednisolone 1g/d for 3 days and taper-Focal edema in brainstem/thalamus.
4	IEC score 0 OR Requires deep stimulus/Stupor/Coma OR Prolonged seizure > 5 min OR Non-convulsive seizures that do not revert OR Motor weakness OR Diffuse cerebral edema/Increased ICT	Mechanical ventilation Methylprednisolone 1g/d for 3 days followed by Taper. Continue steroids till grade 1 Refractory >24h- Additional therapies[5]
5	Tocilizumab	Use if concurrent CRS present

[1] IEC score-

- Orientation: Orientation to year, month, city, hospital: 4 points (1 point each)
- Naming: Name 3 objects (*e.g.*, clock, pen, button): 3 points (1 point each)
- Following commands: (*e.g.*, Show me 2 fingers or close your eyes and stick out your tongue): 1 point
- Writing: Ability to write a standard sentence (*e.g.*, Our national bird is the peacock): 1 point
- Attention: Count backwards from 100 by 10: 1 point

Unarousable or unable to perform IEC assessment is considered as grade 4 ICANS.

[2] Evaluation-

1. MRI Brain with contrast 2. IEC scoring q6h 3. CSF panel- r/o meningoencephalitis 4. EEG
5. Repeat imaging/CSF if symptoms worsen/persist.

[3] **Supportive care-**

1. Aspiration precautions 2. Avoid CNS depressants 3. If no seizures on EEG- use prophylactic Levetiracetam 4. Delirium

[4] **Seizure management-**

Check Seizure protocol

[5] **Additional therapies-**

1. Anakinra- 100mg SC daily for 7 days (Avoid if Cr Clearance <30) (Anakinra checklist)
2. Cyclophosphamide- 1.5g/m^2 One dose (With Mesna 1.5g/m^2 over 24 hours)
3. ATG- 1-2mg/kg/d for D1-3, Premed with steroid and pheniramine, Infuse over 6 hrs

4. DOSAGE FORMS AND STRENGTHS

Dosage Form: Cryopreserved viable CAR-T cells in infusion bag for single dose intravenous infusion (autologous) in 100 ml.

Composition: Each 100ml of cryopreserved cell suspension contains –

1 x 10^8 – 2 x 10^9 anti-CD 19 CAR-T cells, 5% Dimethyl sulfoxide (DMSO), 6% pentastarch, 3.4% human serum albumin (HSA) and 1000 IU Heparin in Plasma-Lyte A solution q.s

Dose: ≥ 5 million CAR-T cells/ kg up to 2 x 10^9 viable CAR-T cells in a single infusion *[see How Supplied/Storage and Handling (14)]*.

5. CONTRAINDICATIONS

None.

6. WARNINGS AND PRECAUTIONS

6.1. Cytokine Release Syndrome

CRS, including fatal or life-threatening reactions, occurred in patients following treatment with NexCAR19. CRS occurred in 68% of patients with relapsed/refractory B-Cell Malignancies receiving NexCAR19, including ≥ Grade 3 (CTCAE v.5.0 grading system) CRS in 6% *[see Adverse Reactions (7)]*.

Key manifestations of CRS in all patients combined included fever, hypotension, tachycardia, chills, hypoxia, headache, and fatigue. Serious events that may be associated with CRS include, cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), renal insufficiency, cardiac failure, respiratory failure, cardiac arrest, capillary leak syndrome, multi-organ failure, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) *[see Adverse Reactions (7)]*.

Only 7% patient required ICU admission. Tocilizumab was administered to 48% patients, median 1 dose (1-4) and Steroids were used in 26% of the patients receiving NexCAR19 Infusion, 4% patients required vasopressor support. 39% of the patients required Intravenous immunoglobulin (IvIg) support. Patients were hospitalized for a median of 8 days (7-19).

No grade 4 or Grade 5 CRS was observed in patients receiving NexCAR19.

Ensure that at least 2 vials of tocilizumab (400mg) are available prior to infusion of NexCAR19 Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling Information (15)]*. At the first sign of CRS, institute treatment with supportive care or tocilizumab, or tocilizumab and corticosteroids as indicated.

6.2. Neurological Toxicities:

No neurological toxicities were observed in patients receiving NexCAR19.

However, a patient must be monitored for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treated promptly.

Patients with active neurological autoimmune or inflammatory disorder should be given NexCAR19 at physician's

discretion.

6.3. Hypersensitivity Reactions

Allergic reactions may occur with the infusion of NexCAR19. Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) in NexCAR19.

Grading and Management of Infusion Reaction

CTCAE Version 5	**Grade I**	**Grade II**	**Grade III**	**Grade IV**	**Grade V**
Definition	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment; prophylactic medications indicated for	Prolonged (not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Management	Continue infusion at same rate; manage symptoms	Reduce infusion rate by 50%; manage symptoms	Interrupt infusion. Manage symptoms, consider steroids if necessary. Rechallenge at 50% rate	Interrupt infusion. Manage symptoms, consider steroids if necessary. Rechallenge at 50% rate	-

6.4. Serious Infections

Severe or life-threatening infections occurred in patients after NexCAR19 infusion. Infections (all grades) occurred in 23% of patients with R/R B - cell Malignancies. Grade 3 or higher infections occurred in 11% of patients, including Grade 3 or higher infections with sepsis in 7%, lung infections in 2%, and sinusitis in 2%. NexCAR19 should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after NexCAR19 infusion and treat appropriately. Administer prophylactic antibacterials according to local guidelines. The use of PCP prophylaxis and prophylaxis of herpes infections is recommended for up to a year post infusion.

Febrile neutropenia was observed in 15% (all grades) of patients with relapsed/refractory B-cell malignancies after NexCAR19 infusion. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated.

6.5. Cytopenia

Cytopenia was observed in all the patients receiving NexCAR19 infusion. All grades Cytopenia included neutropenia (100%), thrombocytopenia (85%), and anemia (98%). Monitor blood counts after NexCAR19 infusion. Cytopenia ≥ Grade 3 was observed which included neutropenia (98%), thrombocytopenia (59%), and anemia (51%).

6.6. Hypogammaglobulinemia

Hypogammaglobulinemia can occur in patients receiving treatment with NexCAR19. Hypogammaglobulinemia was reported as an adverse reaction in 48% of all patients with relapsed/refractory B-cell Malignancies. Monitor immunoglobulin levels after treatment with NexCAR19 and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

Management of Hypogammaglobulinemia –

Sr.No	Check	Action
1	Baseline Immunoglobulin levels	Point 2 - 4
2	Serum IgG level </=400 mg/dL	IVIG replacement- 0.4-0.5g/kg
3	Serum IgG level 400-600 mg/dL	Replace if serious/recurrent infections
4	Serum IgG level >600 mg/dL	Evaluate if serious/recurrent infections
5	Evaluation includes- Total IgG, IgM and IgA CD19+ or CD20+ B-cell counts IgG for S. pneumoniae, Tetanus and Diphtheria	If low, consider IVIG replacement or Test antibody responses to vaccines
6	Follow-up levels	As per the protocol, at least 3-4 weekly
7	Trough IgG level >400 mg/dL	Hold IVIG, monitor Serum IgG levels monthly for 3 months
8	Trough IgG level </= 400 mg/dL	Continue IVIG replacement till 3 months post CART infusion Beyond that monitor levels closely and give IVIG if serious/recurrent infections

6.7. Tumor Lysis Syndrome

TLS can develop after Lymphodepleting Chemotherapy or post NexCAR19 infusion and should be managed as per institutional guidelines.

Please use appropriate TLS prophylaxis according to the individual risk of the patient.

6.8. Cerebral Edema

No episodes of Cerebral Edema were observed in the patients receiving NexCAR19 Infusion. In case of occurrence of Cerebral Edema, following protocol can be followed for management of the same.

Initiate the protocol in case of cerebral edema, raised ICT, decerebrate/decorticate rigidity, 6th nerve palsy or Cushing's triad.

Sr.No.	Action
1	Methylprednisolone 1g/day for 3 days and taper as per the response
2	Head end elevation by 30 degrees
3	Mannitol- 0.5-1g/kg IV followed by 0.25-0.5g/kg q 6hourly Sosm <320 or Osmolal gap <40 OR
4	3% Saline 250ml-15min followed by 50-75 ml/hr Target S Na <155
5	Control Hypertension MAP within 20-25 mm Hg of baseline MAP
6	Metabolic profile 6 hourly
7	CT Brain daily as clinically indicated Or Orbital ultrasound
8	Neurosurgical consult

6.9. Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving NexCAR19 should refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery for at least 8 weeks post infusion.

7. ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions (6.1)]*
- Neurologic Toxicities *[see Warnings and Precautions (6.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (6.3)]*
- Serious Infections *[see Warnings and Precautions (6.4)]*
- Cytopenia *[see Warnings and Precautions (6.5)]*
- Hypogammaglobulinemia *[see Warnings and Precautions (6.6)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (6.7)]*
- Cerebral Edema *[see Warnings and Precautions (6.8)]*

8. CLINICAL TRIALS EXPERIENCE

The data described in the *WARNINGS AND PRECAUTIONS (6)* reflect exposure to a single dose of NexCAR19 in open-label Phase I and Phase II studies conducted with 64 patients diagnosed with relapsed or refractory B-cell Malignancies.

Refer section *CLINICAL STUDIES (13)* for detailed information.

9. USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary

There are no available data with NexCAR19 use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with NexCAR19 to assess whether it can cause fetal harm when administered to pregnant woman. It is not known if NexCAR19 has the potential to be transferred to the fetus. Therefore, NexCAR19 is not recommended for women who are pregnant, and pregnancy after NexCAR19 infusion should be discussed with the treating physician.

9.2 Lactation

Risk Summary

There is no information regarding the presence of NexCAR19 in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NexCAR19 and any potential adverse effects on the breastfed infant from NexCAR19or from the underlying maternal condition.

9.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually active females of reproductive potential should have a pregnancy test prior to starting treatment with NexCAR19.

Contraception

There is no data to provide a recommendation concerning duration of contraception following treatment with NexCAR19.

Infertility

There are no data on the effect of NexCAR19 on fertility.

10. DESCRIPTION

NexCAR19 is a CD19-directed genetically modified autologous T-cells for Relapsed/Refractory B-cell Lymphomas and Relapsed/ Refractory B-cell Acute Lymphoblastic Leukemia. The CAR consists of a humanized single chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T cell activation and antitumor activity while 4-1BB enhances the expansion and persistence of CAR-T. Upon binding to CD19 expressing cells, the CAR transmits a signal to promote T cell expansion, activation, target cell elimination and persistence of CAR-T.

Chimeric antigen receptor T-cell therapy (CAR T) is a form of immunotherapy that is considered a breakthrough innovation for B-cell malignancies. In this therapy, the patients' own white blood cells (Known as T-cells) are removed and modified so that they become effective in targeting and killing the cancer cells.

Qualitative and Quantitative Composition of NexCAR19	
Description	***Specification***
General Characteristics	Milky
Components	Genetically modified autologous T-cells suspension in infusion bag(s)
Product Modified	Yes
Type of Product Modification	Genetic modification by CAR encoding lentiviral vector

Dosage	Dosage Form: Cryopreserved viable CAR-T cells in infusion bag for single dose intravenous infusion (autologous) in 100 ml Dose: ≥ 5 million CAR-T cells/ kg up to 2 x 10^9 viable CAR-T cells in a single infusion
Dosage Frequency	Single intravenous infusion
Composition of the formulation	Each 100 ml of cryopreserved cell suspension contains: 1 x 10^8 - 2 x 10^9 anti-CD19 CAR-T cells 5% Dimethyl sulfoxide (DMSO), 6% pentastarch, 3.4% human serum albumin (HSA) and 1000 IU Heparin in Plasma-Lyte A Solution q.s
Packaging material	Infusion bag(s)
Sterility	Sterile
Shelf - Life	The shelf life of the cryopreserved cell suspension of NexCAR19 is 3 months from the time of manufacturing, when the infusion bag containing the product overwrapped in a sterile bag, placed in an aluminium cassette is stored at temperature ≤ -80ºC.

11. CLINICAL PHARMACOLOGY

11.1. Mechanism of Action

NexCAR19 involves genetic modifications of the patient's own T cells with a transgene. These CAR T cells identify and eliminate CD19-positive malignant B cells. Since the CAR T product identifies all the CD19-positive malignant cells, the mechanism of action of CD19 specific CAR T cells is the same for all the disease indications.

11.2. Pharmacodynamics

NexCAR19 is an intravenous therapy. Once NexCAR19 is infused in the patient it starts circulating in the blood system. NexCAR19 identifies CD19 positive B cells and upon interaction it causes activation and expansion of CAR T cells. During these cascades of events, patients usually have symptoms like fever, nausea, mild fatigue and hypotension which is managed depending on the severity of the symptoms. CAR copies keep multiplying and killing CD19 positive B cells. Response assessment of NexCAR19, its expansion and persistence in the circulatory system is measured by PCR and/or flow cytometry.

11.3. Pharmacokinetics

Absorption: NexCAR19 are administered as an IV infusion. Therefore, absorption studies are not performed as they aren’t relevant to this type of product.

Distribution: NexCAR19 has been designed against CD19 positive hematological malignancies. When infused in a patient's body, the CAR T cells migrate to the entire body, identifying and killing CD19 positive B-cells in blood.

Metabolism: The anticipated metabolic products of NexCAR19, a human autologous T-cell product, are typical cellular degradation products resulting from normal cellular clearance mechanisms.

Excretion: Elimination of T cells from the body is not regulated by excretion; rather by physiological processes such as T-cell apoptosis. Thus, standard excretion pharmacokinetic analysis techniques do not apply.

12. NONCLINICAL TOXICOLOGY

12.1. Pharmacology:

NexCAR19 constitutes autologous T-cells that are genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor. To determine functional efficacy, the NexCAR19 were administered into immunodeficient NOD/SCID mice bearing CD19+ cell-lines and tumor burden was monitored. Significant reduction in tumor was observed after NexCAR19 treatment.

12.2. Toxicology:

Studies involving single dose with NexCAR19 were performed using serum hematology and serum biochemistry profile along with histopathology of vital organs. NALM6 was used as the control group and NOD/SCID mice were used as the NexCAR19 treated group. No abnormalities were observed in hematology and biochemistry profiles. No significant aberrations were observed in NexCAR19 treated NOD/SCID mice.

13. CLINICAL STUDIES

The data described in the *WARNINGS AND PRECAUTIONS (6)* reflect exposure to a single dose of NexCAR19 in Open-Label Phase I and Phase II studies with 64 patients diagnosed with relapsed or refractory B-cell Malignancies.

Relapsed or Refractory B-cell Malignancies

A total of 64 patients with r/r High grade B - lymphoma (43), B – Acute Lymphoblastic Leukemia (B-ALL) (17) and B - lymphomas (4) were enrolled in two Phases (Phase I; 06/2021 till 06/2022 and Phase II; 12/2022 till 08/2023), 62 out of 64 underwent leukapheresis and 54 received NexCAR19 in Phase 1 (n=10) and Phase II (n = 44). 48 patients received the target dose in Phase I (n= 7) and Phase II (n = 41). The median age was 43 years (16-71) with 50 (78%) male patients. Patients had a median of 2 prior lines of therapy (1-6), 75% had refractory disease, 23% of lymphoma patients had bulky disease, and the median bone marrow blast percentage was 61% (5-98%) in the B-ALL cohort. The median vein-to-vein time was 17 (7-132) days. 48 patients reached Day 28 time point in Phase I and Phase II trial. The ORR of Phase I and Phase II was 67% (32/48), including 52% (25/48) with a CR+ CRi and 15% (7/48) with PR.

None of the patients developed ICANS of any grade. CRS developed in 68% cases (grade 1/2 in 60%, ≥ grade 3 in 5%). Grade 3/4 cytopenias developed in 100% cases. The median duration of neutropenia was 7 (4-32) days. Only (7%) patient required ICU admission. Tocilizumab was administered to 48% patients, median 1 dose (1-4) and Steroids were used in 26% of the patients receiving NexCAR19 Infusion, 4% patients required vasopressor support. 39% of the patients required IvIg support. Patients were hospitalized for a median of 8 days (7-19).

Table 3 summarizes list of adverse reactions in patients treated with NexCAR19 in Phase I and Phase II trial (N=54)

Toxicities	Grade III/IV	All Grades
Adverse Events of Special Interest		
Cytokine Release Syndrome	3 (6%)	36 (68%)
ICANS	0 (0%)	0 (0 %)
Hypogammaglobulinemia	-	26 (48%)
Hematological		
Anemia	27 (51%)	52 (98%)
Neutropenia	52 (98%)	53 (100%)
Thrombocytopenia	28 (59%)	45 (85%)
Febrile Neutropenia	7 (13%)	8 (15%)
Non-Hematological		
Abdominal Pain	1 (2%)	1 (2%)

Diarrhea	1 (2%)	6 (11%)
Pain	1 (2%)	1 (2%)
Disease Progression	1 (2%)	3 (6%)
Lung infection	1 (2%)	2 (4%)
Sepsis	4 (7%)	5 (9%)
Pneumonia	0 (0%)	1 (2%)
Sinusitis	1 (2%)	1 (2%)
Ejection Fraction Decreased	1 (2%)	1 (2%)
Alanine Aminotrasferase Increased	1 (2%)	4 (7%)
Alkaline Phosphatase increased	2 (4%)	9 (17%)
Bilirubin increased	1 (2%)	2 (4%)
Hyponatremia	1 (2%)	20 (38%)
Hypocalcemia	2 (4%)	28 (53%)
Hypokalemia	2 (4%)	14 (26%)
Syncope	1 (2%)	1 (2%)
Hypotension	1 (2%)	7 (13%)
Tumor hemorrhage	1 (2%)	1 (2%)
Heart Failure	1 (2%)	1 (2%)

Other clinically important adverse reactions that occurred in less than 10% of patients treated with NexCAR19include the following:

- *Cardiac disorders:* Cardiac failure (2%)
- *Infections and infestations:* Pneumonia (2%), Sepsis (7%).
- *Respiratory, thoracic and mediastinal disorders:* Dyspnea (4%),

14. SUPPLIED/STORAGE AND HANDLING

14.1. Storage:

Storage conditions: ≤ -80 degree Celsius

14.2. Special precautions for handling:

- Confirm patient's identity upon receipt of the product. Confirm Patient ID prior to infusion and verify Patient ID in a conspicuous manner.
- The expiry date is indicated on the product label. The shell life of the product is 3 months.
- Do not thaw the product until it is ready to be used. NexCAR19 must be kept out of the reach and sight of children.
- Use closed, leak-proof, break-proof containers while transporting infusion bag(s) within the facility.
- Aseptic Conditions: Proper Aseptic conditions should be followed while thawing and handling the product.

14.3. Special Precautions for disposal:

- Any unused product or waste material should be disposed of in accordance with biomedical waste management guidelines of the healthcare centre.
- NexCAR19 products should be transported within the facility in closed, break-proof, leak-proof containers.

14.4. Solid and liquid waste:

All material having been in contact with Autologous HCAR19 should be handled and disposed of as potentially infectious waste in accordance with local hospital procedures.

15. PATIENT COUNSELING INFORMATION

Advise the patient to read CDSCO approved Medication guide to know more about the NexCAR19 **(Appendix A: Medication Guide)**

1. Ensure that the patient understands the risk of manufacturing failure.
2. Advise the patient to avoid intake of any steroids and chemotherapy treatment at least 24 hours prior to apheresis procedure and NexCAR19 infusion.
3. Advise patients to immediately report signs and symptoms like fever, nausea, diarrhoea, dizziness, fatigue, lethargy, difficulty concentrating, agitation, tremor; and consult his/her treating physician for the management of the same.
4. Female patients should inform their treating physician in advance if they are pregnant or planning a pregnancy or they are lactating. It is advised not to use the medication during pregnancy or lactating.
5. Advise patients not to take other medication without consulting with the treating physician.
6. Patients are instructed to receive irradiated blood products if at all indicated for use, post NexCAR19 infusion.

Details of Manufacturer:

Immunoadoptive Cell Therapy Private Limited (ImmunoACT)
1st Floor, Plot no R-977, TTC Industrial Area, MIDC, Rabale Navi Mumbai 400701, India.

APPENDIX A: Medication Guide

MEDICATION GUIDE

NexCAR19 (Actalycabtagene autoleucel)
(Genetically modified Autologous T cells)

Read this Medication Guide before you start your NexCAR19 treatment. The more you know about your treatment, the more active you can be in your care. Talk with your treating physician if you have questions about your health condition or treatment. Reading this Medication Guide does not take the place of talking with your treating physician about your treatment.

What is the most important information I should know about NexCAR19?

NexCAR19 may cause side effects that are severe or life-threatening. Call your treating physician or get emergency help right away if you get any of the following:

- Difficulty breathing
- Fever (100.4°F/38°C or higher)
- Chills/shaking chills
- Confusion
- Severe nausea, vomiting, diarrhea
- Severe muscle or joint pain
- Difficulty concentrating
- Dizziness
- Fatigue

It is important that you tell your treating physicians that you have received NexCAR19 Your treating physicians may give you other medicines to treat your side effects.

NexCAR19 is not recommended for pregnant and lactating women. Pregnancy after NexCAR19infusion must be discussed with the treating physician.

What is NexCAR19?

NexCAR19 is a genetically modified autologous product, a form of immunotherapy that is considered a breakthrough innovation for B-cell malignancies. In this therapy, the patients' own white blood cells (Known as T-cells) are collected and modified in the laboratory so that they become effective in targeting and killing the cancer cells.

How will I get NexCAR19?

Since NexCAR19 is made from your own white blood cells, your treating physician has to take some of your blood. This is called “leukapheresis.” It can take up to 3 to 4 hours and may need to be repeated. Blood for leukapheresis will be collected through peripheral vein or by using the central line.

Your blood cells are sent to the manufacturing site to make NexCAR19. It takes about 2-3 weeks from the time your cells are received at the manufacturing site and shipped back to your treating physician, but the time may vary.

While waiting for NexCAR19 to be made, your treating physician may give you therapy to stabilize your cancer. In addition, before you get NexCAR19, your treating physician may give you chemotherapy for a few days to prepare your body. Your physician will examine you for the suitability of NexCAR19 infusion. The infusion takes less than one hour. You should plan to stay within 2 hours from the hospital after receiving the NexCAR19 for at least 4 weeks.

What should I avoid after receiving NexCAR19?

- Do not drive, operate heavy machinery, or participate in any adventure activity or sports for approximately 8 weeks after you get NexCAR19 because the treatment can cause temporary memory and coordination problems, including sleepiness, confusion, weakness, dizziness, and seizures.
- Do not donate blood, organs, tissues, sperm, oocytes, and other cells without consulting your treating physician.

What are the possible or reasonably likely side effects of NexCAR19?

The most common side effects of NexCAR19 are:

- Fever (100.4°F/38°C or higher)
- Difficulty breathing
- Very low blood pressure
- chills/shaking chills
- confusion
- Nausea, vomiting, diarrhea
- Muscle or joint pain
- dizziness
- headache

Tell your treating physician right away if you develop fever, chills, or any signs or symptoms of an infection. Call your doctor for medical advice about any side effects.

General information about the safe and effective use of NexCAR19 -

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use NexCAR19 for a condition for which it was not prescribed. Talk to your treating physician about any concerns.

Manufactured and Distributed by: Immunoadoptive Cell Therapy Private Limited (ImmunoACT)

1st Floor, Plot no R-977, TTC Industrial Area, MIDC, Rabale Navi Mumbai 400701, India.