TECHNICAL SPECIFICATIONS

NATURAL KILLER

HETERÓLOGAS

GC
GENCELL
BIOTECHNOLOGY

Gencell® Natural Killer Cells

NATURAL KILLER HETEROLOGOUS
Heterologous Natural Killer Cells.

PRODUCT NAME
NATURAL KILLER HETEROLOGOUS.

COMPOSITION
The solution contains:
Heterologous Natural Killer (NK) cells pretreated with Nivolumab (1.35 mg), single presentation composed of:
7 million heterologous NK cells

PHARMACEUTICAL FORM AND USAGE CONSIDERATIONS
Injectable solution.

PRESENTATION
The plastic container protects the monovette containing 4 mL of product.

THERAPEUTIC PROPERTIES

Mechanism of Action

Natural Killer (NK) cells are essential components of the innate immune system, with the ability to recognize and eliminate tumor cells and virally infected cells. In the bloodstream, NK cells recirculate and migrate toward areas showing alterations in MHC-I (Major Histocompatibility Complex Class I) expression. The detection of such abnormalities signals the presence of tumor or infected cells, activating NK cells to initiate a proteolytic degranulation process.

Compared to autologous NK cells, heterologous NK cells offer a consistent functional profile and enhanced activity in cancer immunotherapy. Autologous NK cells often show variable efficacy depending on the patient's health status and the immunosuppressive tumor microenvironment. Therefore, heterologous NK cells are an ideal alternative for patients with hematological disorders or cancer undergoing immunosuppressive treatments such as chemotherapy, where autologous NK cell activity may be reduced.

These heterologous NK cells are isolated from healthy donors and expanded in vitro to achieve greater cytotoxic activity and improved antitumor efficacy. NK cells recognize and destroy tumor cells through the detection of reduced MHC-I expression and other cellular stress signals. Upon detection, NK cells undergo degranulation, releasing cytotoxic granules containing perforins and granzymes, which induce apoptosis in target cells.

This degranulation also facilitates the release of tumor antigens, which dendritic cells in the tumor microenvironment capture and present to T lymphocytes, promoting a specific adaptive immune response against the tumor.

Pretreatment with Nivolumab blocks the interaction between the programmed death receptor (PD-1) and its ligands PD-L1 and PD-L2 on tumor cells. Inhibiting this PD-1/PD-L1 pathway:

- Allows T and NK cells to recognize and attack tumor cells previously protected by PD-L1 expression.
- Enhances the cytotoxic capacity of heterologous NK cells to identify and destroy tumor cells.
- Promotes a more robust antitumor immune response.

The combination of heterologous NK cells with Nivolumab offers a significant advantage by overcoming tumor immune evasion mechanisms, increasing tumor visibility to the immune system, and reducing tumor growth. This approach not only optimizes the immune response against resistant tumors but also facilitates the development of an adaptive immune memory that contributes to long-term remission and cancer control.

CLINICAL DATA

a.Therapeutic Indications

The combined therapy of heterologous NK cells and Nivolumab has shown effectiveness in treating several malignancies, including: Non–Small Cell Lung Cancer (NSCLC), Melanoma, Diffuse Large B-Cell Lymphoma (DLBCL), Acute Lymphoblastic Leukemia (ALL), Renal Cancer, Metastatic and Triple-Negative Breast Cancer (TNBC), Prostate Cancer, Pancreatic Cancer

The efficacy of this combination results from the ability of heterologous NK cells to identify and destroy tumor cells, combined with Nivolumab's role in amplifying this immune response.

b. Dosage and Method of Administration

Intravenous route. Cannulate the patient with 100 mL of 0.9% saline solution and ensure proper venous access. Then retrieve the content of the monovette and administer it using the Y-connector of the venoclysis set slowly (not as a bolus). Continue the infusion with the remaining saline solution over approximately 15 minutes.

c.Contraindications
Sensitivity or allergy to any component of the formula..

d. Warnings and Precautions
No evidence is available regarding safety in children under 12 years of age. Administration must be performed under strict medical supervision, especially during the first 24–48 hours after application.
Immune-mediated adverse reactions have been reported, including severe or fatal events that may occur in any organ or tissue expressing PD-1 or PD-L1 monoclonal antibodies.
The product may contain traces of RPMI medium.

e.Interactions

Concurrent use of immunosuppressants or corticosteroids (such as cyclosporine) should be avoided during NK cell and Nivolumab therapy, as these agents may reduce treatment efficacy by suppressing the immune response necessary for its mechanism of action.
Certain chemotherapy agents can negatively affect NK cell activity by compromising viability and function. Sequential planning of chemotherapy and NK/Nivolumab therapy is crucial to minimize adverse effects.
• Anthracyclines (e.g., Doxorubicin, Epirubicin) may increase toxicity risk when combined with Nivolumab.
• Antimetabolites (e.g., Methotrexate, 5-Fluorouracil) can interfere with NK cell proliferation and tumor response, reducing cytotoxic capacity.
• Topoisomerase inhibitors (e.g., Irinotecan, Topotecan, Etoposide) may induce DNA damage and cellular stress, affecting NK function and increasing the likelihood of adverse effects.
• Alkylating agents (e.g., Cyclophosphamide, Ifosfamide, Melphalan) can cause significant myelosuppression, decreasing NK production and activity, and potentially compromising Nivolumab efficacy by reducing immunocompetent cell numbers.

f. Pregnancy and Lactation
Use of this product is not recommended during pregnancy or lactation. Due to the physiological conditions in these stages, treatment may pose fetal risk or alter milk production and composition.
Increased NK cell levels could lead to complications in fetal development or during lactation.
If no therapeutic alternative is prescribed, close monitoring of the infant for potential adverse effects or feeding issues is required.

g. Adverse Effects
Possible symptoms include dizziness, nausea, fainting, headache, vomiting, mild fever (<38°C), fatigue, or muscle pain, which usually resolve spontaneously within 24–48 hours post-administration.
Though rare, hypersensitivity reactions such as urticaria or rash may occur.
Tumor lysis syndrome is also possible, resulting from a temporary increase in proinflammatory cytokines, which may cause high fever, hypotension, or flu-like severe symptoms.

ADDITIONAL DATA

a. List of Excipients
0.9% saline solution.

b. Shelf Life
After receipt, the product must be administered immediately or within no more than 24 hours.

c. Storage and Preservation Conditions
Store in a place protected from direct sunlight and keep refrigerated between 2 and 8 °C. Do not expose to radiation or heat sources. Avoid freezing or shaking.

Keep out of reach of children and pets.

d. Waste Management
Use chemotherapy waste containers and deliver them to the authorized collection service.
Freezing or prolonged refrigeration beyond the recommended period reduces product viability and may increase the likelihood of side effects.

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