TECHNICAL SPECIFICATIONS

NATURAL KILLER
DOBLE BLOQUEO
AUTÓLOGAS

GC
GENCELL
BIOTECHNOLOGY

Gencell® NATURAL KILLER

NATURAL KILLER DOUBLE BLOCK AUTOLOGOUS

Autologous Natural Killer cells.

PRODUCT NAME

NATURAL KILLER BLOCKADE AUTOLOGOUS

COMPOSITION

The solution contains:

Autologous Natural Killer cells pretreated with Nivolumab and Ipilimumab, a single formulation composed of:
7 million autologous NK cells

PHARMACEUTICAL FORM AND USAGE CONSIDERATIONS

Injectable solution.

PRESENTATION

The plastic container protects the single-serve vial, which contains 4 ml of the product.

THERAPEUTIC PROPERTIES

Mechanism of action

The mechanism of action of autologous NKs-DB, which combines autologous NK cells pretreated with nivolumab and ipilimumab, is based on the activation and optimization of both the innate and adaptive immune systems to combat tumor cells.

NK cells play a crucial role in the innate immune system. These cells recognize and destroy tumor cells that present MHC-I abnormalities, indicating that the cell has undergone malignant transformation. When NK cells detect these abnormalities, they release cytotoxic granules containing perforins and granzymes, which perforate the tumor cell membrane and trigger apoptosis.

Furthermore, the release of tumor antigens during this process stimulates antigen presentation by dendritic cells, which activates T lymphocytes of the adaptive immune system to generate a specific response against the tumor.

Pretreatment with nivolumab (a PD-1 inhibitor) blocks the interaction between the PD-1 receptor on NK and T cells with their ligands PD-L1 and PD-L2 present on tumor cells, thereby eliminating one of the main immune evasion mechanisms that tumors use to inhibit cytotoxic activity. This allows NK and T cells to regain their ability to recognize and destroy tumor cells previously inaccessible to the immune system.

Ipilimumab, on the other hand, is a monoclonal antibody that inhibits CTLA-4, a regulatory protein that suppresses T cell activation. By blocking this pathway, ipilimumab enhances T cell activation, promoting a more aggressive and prolonged response against cancer cells. Inhibiting CTLA-4 favors early T cell activation in the lymph nodes, allowing for clonal expansion of specific T cells capable of attacking tumors that have evaded the immune response. The combination of both therapies enhances the immune system's ability to attack both the innate (NK cells) and adaptive (T cells) domains, resulting in increased tumor visibility, reduced growth, and, in some cases, prolonged remission.

CLINICAL DATA

a.Therapeutic Indications

The combination of autologous NK cells pretreated with nivolumab and ipilimumab has been shown to be effective in a wide range of malignancies, including metastatic melanoma, non-small cell lung cancer (NSCLC), advanced renal cell cancer, recurrent or metastatic head and neck cancer, metastatic colorectal cancer with microsatellite instability, and malignant pleural mesothelioma. This combination increases the survival rate of NK cells and provides an innovative therapeutic option for patients with refractory or advanced tumors.

b. Dosage and Administration

intravenous. Inject the patient with 100 milliliters of 0.9% saline solution and ensure proper placement. Then, retrieve the contents of the monovette and administer it slowly (not as a bolus) using the IV set's Y connector. The remaining saline solution is administered over 15 minutes.

c. Contraindications

Sensitivity or allergies to any component of the formula.

d. Warnings and Precautions

There is no evidence in children under 12 years of age.
Administration should be carried out under strict medical supervision, especially during the first 24 to 48 hours after application.
Immune-mediated adverse reactions, including serious or fatal events, have been reported and can occur in any organ system or tissue; these reactions usually occur during treatment but may manifest after discontinuation.
May contain traces of RPMI medium.

.

e. Interactions
Avoid the concomitant use of immunosuppressants or corticosteroids during therapy with NK cells, nivolumab, and ipilimumab, such as cyclosporine, as they may reduce treatment efficacy by inhibiting the immune response, an essential component of the action of these drugs. Both drugs rely on immune activation to enhance tumor cell destruction, and immunosuppressants can counteract this effect. Certain chemotherapy agents can negatively affect NK cell activity by decreasing their viability and function. The sequential administration of chemotherapy and NK cell/nivolumab/ipilimumab therapy should be carefully planned to avoid adverse interactions. Anthracyclines such as doxorubicin and epirubicin may increase the risk of toxicity when combined with nivolumab and ipilimumab, as both drugs can aggravate the effects on the immune and cardiovascular systems.

Antimetabolites such as methotrexate and 5-fluorouracil can decrease the proliferation capacity of NK cells and their cytotoxic function, compromising the immune response. Topoisomerase inhibitors such as irinotecan, topotecan, and etoposide can cause DNA damage and cellular stress, which could interfere with NK cell function and increase the risk of toxicity in combination with these immunotherapeutics. Finally, alkylating agents such as cyclophosphamide, ifosfamide, and melphalan cause significant myelosuppression, which decreases the number of immunocompetent cells available, reducing the efficacy of the therapeutic combination.

f. Pregnancy and breastfeeding.
Evidence suggests that the use of this product is not recommended during pregnancy and breastfeeding. Due to the specific physiological conditions at these stages, use of the medication may pose a risk to the fetus and alter milk production or composition. An increase in NK cells could cause complications both in fetal development and during breastfeeding. If an alternative to this therapy is not prescribed, the infant should be monitored for adverse effects and/or adequate milk intake.

g. Adverse effects.
Vertigo, nausea, fainting, headache, vomiting, low-grade fever (temperature <38°C), fatigue, or myalgia may occur, which usually resolve spontaneously within 24–48 hours after application. Hypersensitivity reactions, although rare, may include urticaria or a skin rash. There is a risk of tumor lysis syndrome due to a transient increase in proinflammatory cytokines, which can cause high fever, hypotension, and severe flu-like symptoms.

More severe immune-related adverse effects may also occur, such as colitis, hepatitis, pneumonitis, and hypophysitis, as well as dermatitis, pruritus, and endocrine toxicities such as hypothyroidism or adrenal insufficiency, which require prompt medical monitoring and management.

These immune-related effects are due to the inhibition of immune checkpoints, such as PD-1 and CTLA-4, which enhances the immune system's activity not only against tumor cells but also against healthy tissues, causing inflammation in organs such as the intestine, lungs, and endocrine glands. In combination therapies with nivolumab and ipilimumab, the rate of immune-related adverse effects varies depending on the type of cancer and treatment regimen, but in general, approximately 55–60% of patients receiving this combination experience some type of immune-related adverse effect.

ADDITIONAL DATA

a. List of excipients.
Saline solution 0.9%

b. Shelf life.
After receiving the product, it must be administered immediately or within 24 hours.

c. Storage and preservation conditions.
Store away from direct sunlight and refrigerate between 2 and 8°C. Do not expose to sources of radiation or fire. Avoid freezing and shaking. Keep out of reach of children and pets.

d. Waste management.
Containers for chemotherapy waste must be used, and the waste must be delivered to the collection service.
Freezing or refrigeration for longer than recommended reduces the viability of the product, which can increase the risk of side effects.

Marketing authorisation holder.
Gencell®