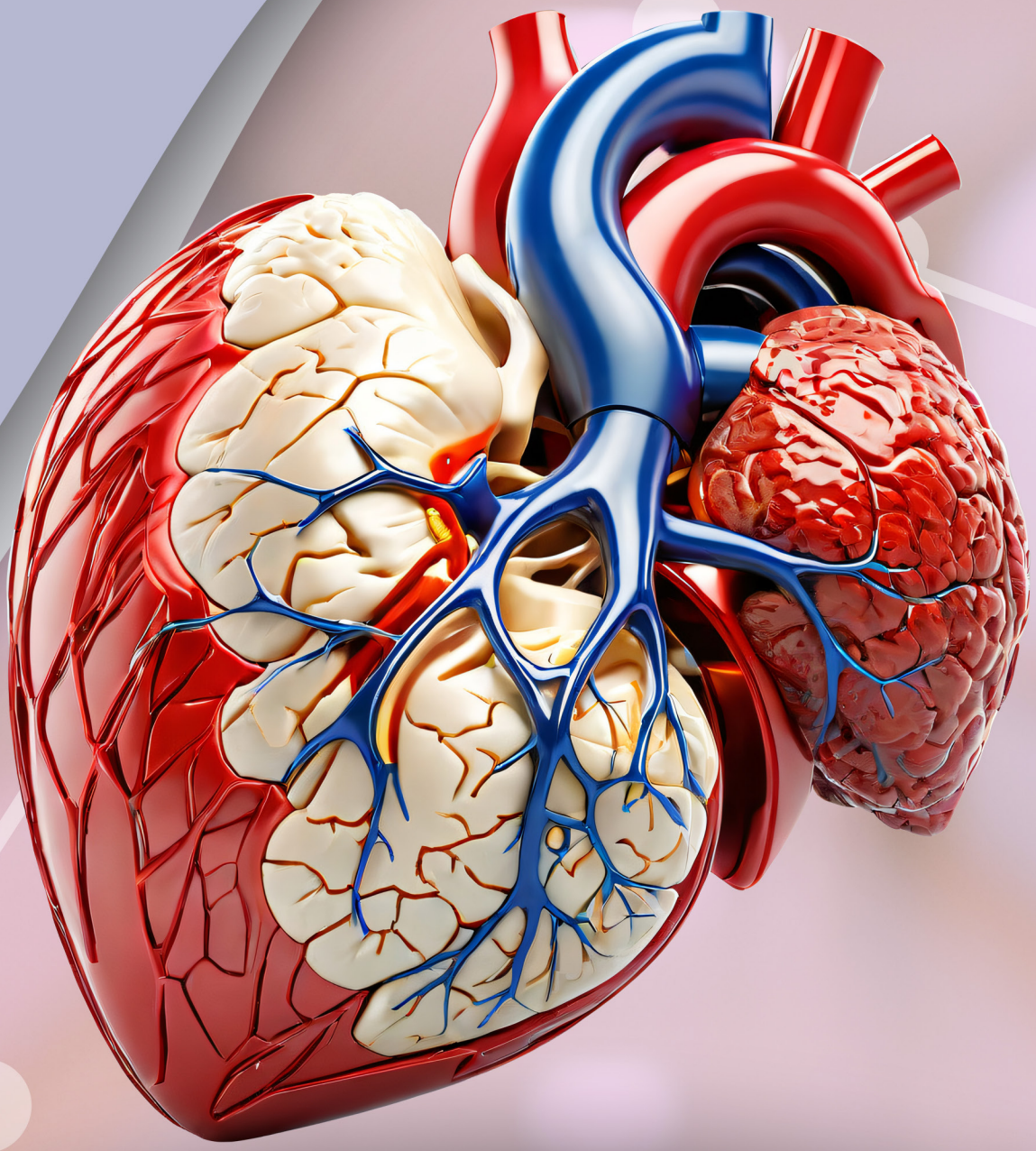
TECHNICAL SPECIFICATIONS



NATURAL KILLER
DOBLE BLOQUEO
HETERÓLOGAS

GC
GENCELL
BIOTECHNOLOGY

Gencell® NATURAL KILLER

NATURAL KILLER DOUBLE HETEROLOGOUS BLOCKADE

PRODUCT NAME
NATURAL KILLER DOUBLE HETEROLOGOUS BLOCKADE

COMPOSITION
The solution contains:
Heterologous Natural Killer cells pretreated with Nivolumab and Ipilimumab, a single formulation composed of:
7 million heterologous 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 heterologous NK-DB, which combines heterologous NK cells pretreated with nivolumab and ipilimumab, is based on the enhancement of the innate and adaptive immune systems to combat tumor cells.

NK (Natural Killer) cells are essential in the innate immune system, responsible for identifying and eliminating tumor cells and infected cells. In the bloodstream, these cells target areas with altered MHC-I (Major Histocompatibility Complex Class I) expression. A reduction in MHC-I expression indicates the presence of malignant cells, which activates NK cells to initiate degranulation and release cytotoxic granules containing perforins and granzymes. These granules induce tumor cell apoptosis and facilitate the release of tumor antigens, which are processed and presented by dendritic cells to T lymphocytes, promoting a tumor-specific adaptive immune response. Heterologous NK cells, obtained from healthy donors and expanded in vitro, offer consistency in their functional profile and greater cytotoxic activity compared to autologous NK cells, which can exhibit significant variability in efficacy due to factors such as the patient's health status and immunosuppression induced by the tumor microenvironment. This makes them an ideal option for patients with hematological disorders or those who have received treatments that affect their immune system, such as chemotherapy. Pretreatment with nivolumab, a PD-1 receptor inhibitor, blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2 on tumor cells.

This inhibition eliminates one of the tumor's main immune evasion mechanisms, allowing NK and T cells to recognize and attack previously protected tumor cells. Nivolumab thus enhances the ability of heterologous NK cells to destroy tumor cells and strengthens the overall immune response. Ipilimumab, for its part, acts as an inhibitor of the CTLA-4 receptor on T cells. By blocking CTLA-4, ipilimumab increases the activation and proliferation of cytotoxic T cells, enhancing the immune response against tumor cells and complementing the action of NK cells. The combination of nivolumab and ipilimumab, along with heterologous NK cells, significantly improves the immune system's ability to overcome tumor evasion mechanisms, increase tumor visibility, and reduce tumor growth. This comprehensive approach facilitates a robust immune response and may contribute to long-term remission and control of malignancies.

CLINICAL DATA
a. Therapeutic Indications
Combination therapy with heterologous NK cells pretreated with nivolumab and ipilimumab has been shown to be effective in the treatment of various malignancies, including non-small cell lung cancer (NSCLC), melanoma, large B-cell lymphoma (DLBCL), acute lymphoblastic leukemia (ALL), renal cancer (including renal cell carcinoma such as clear cell carcinoma and transitional cell carcinoma), metastatic and triple-negative breast cancer (TNBC), advanced prostate cancer, and pancreatic cancer (including pancreatic ductal adenocarcinoma). Heterologous NK cells, obtained from healthy donors, are combined with nivolumab and ipilimumab to enhance the patient's immune system's ability to attack tumor cells. This combination harnesses the intrinsic ability of NK cells to identify and destroy malignant cells, while nivolumab and ipilimumab enhance this immune response by inhibiting specific immune inhibitory checkpoints.

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.

e. Interactions

The simultaneous use of immunosuppressants or corticosteroids, such as cyclosporine, should be avoided during treatment with NK cells, nivolumab, and ipilimumab, as these drugs can reduce the effectiveness of the treatment by inhibiting the immune response, which is crucial for the action of these drugs. Since both nivolumab and ipilimumab rely on immune activation to enhance tumor cell destruction, immunosuppressants can counteract this effect.

Certain chemotherapy drugs can negatively affect NK cell activity by compromising their viability and function. Therefore, it is important to carefully plan the sequential administration of chemotherapy with NK cells/nivolumab/ipilimumab to avoid adverse interactions. Anthracyclines, such as doxorubicin and epirubicin, may increase the risk of toxicity when combined with nivolumab and ipilimumab, as they may intensify the negative effects on the immune and cardiovascular systems. Antimetabolites, such as methotrexate and 5-fluorouracil, can reduce the proliferative and cytotoxic capacity of NK cells, impairing the immune response. Topoisomerase inhibitors, such as irinotecan, topotecan, and etoposide, can damage DNA and cause cell stress, which could interfere with NK cell function and increase the risk of toxic effects when used in conjunction with these immunotherapeutics. Finally, alkylating agents, such as cyclophosphamide, ifosfamide, and melphalan, induce significant myelosuppression, reducing the number of immunocompetent cells and potentially diminishing the efficacy of combination therapy.

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.

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g. Adverse effects.

Side effects such as vertigo, nausea, syncope, headache, vomiting, low-grade fever (temperature below 38°C), fatigue, or myalgia may occur, usually resolving spontaneously within 24 to 48 hours after application. Although less common, hypersensitivity reactions may manifest as hives or skin rashes. There is a risk of tumor lysis syndrome, which occurs due to a temporary increase in proinflammatory cytokines and can cause high fever, hypotension, and flu-like symptoms. More serious immune-related adverse effects may also occur, such as colitis, hepatitis, pneumonitis, and hypophysitis, as well as dermatitis, pruritus, and endocrine problems such as hypothyroidism or adrenal insufficiency, which require appropriate medical supervision and treatment. These immune-related adverse effects result from the inhibition of immune checkpoints such as PD-1 and CTLA-4, which intensifies the immune system's response not only against tumor cells but also against healthy tissues, causing inflammation in organs such as the gut, lungs, and endocrine glands. The incidence of immune-related adverse effects in combination therapies with nivolumab and ipilimumab may vary depending on the type of cancer and treatment regimen, but overall, 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