PRODUCT SUMMARY

1. Trade name of the medicinal product

NORSK - NO DATA

2. Qualitative and quantitative composition

NORSK - NO DATA

3. Pharmaceutical form

NORSK - NO DATA

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

LEUCOMAX IS INDICATED TO REDUCE THE RISK OF INFECTION AND TO ALLOW BETTER ADHERENCE TO THE CHEMOTHERAPEUTIC REGIMEN BY DECREASING THE SEVERITY OF CYTOTOXIC CHEOMOTHERAPY-INDUCRED NEUTROPENIA.
LEUCOMAX IS INDICATED FOR THE ACCELERATION OF MYELOID RECOVERY IN PATIENTS FOLLOWING AUTOLOGOUS OR SYNGENEIC BONE MARROW TRANSPLANTATION.
LEUCOMAX IS NOT INTENDED TO IMPROVE OVERALL SURVIVAL OR INCREASE TIME TO RELAPSE.
LEUCOMAX IS INDICATED AS ADJUVANT THERAPY IN GANCYCLOVIR (DHPG) - INDUCED NEUTROPENIA IN PATIENTS WITH AIDS-RELATED CYTOMEGALOVIRUS (CMV) RETINITIS IN ORDER TO MAINTAIN RECOMMENDED DHPG DOSAGE.

4.2 Posology and Method of Administration

LEUCOMAX DOSING REGIMENS VARY ACCORDING TO THE INDICATION FOR THERAPY. LEUCOMAX MUST BE RECONSITUTED BEFORE ADMINISTRATION. THE MAXIMUM DAILY DOSE OF LEUCOMAX SHOULD NOT EXCEED O.11 MILLION IRU/KG. THE RECOMMENDED DOSAGE REGIMENS ARE:
CANCER CHEMOTHERAPY - 0.06-0.11 MILLION IRU/KG/DAY - 5 TO 10 MICROGRAMS/KG/DAY ADMINISTERED SUBCUTANEOUSLY. TREATMENT SHOULD BE INITIATED 24 HOURS AFTER THE LAST DOSE OF CHEMOTHERAPY AND CONTINUED FOR 7 TO 10 DAYS DOSING MAY BE INITIATED AT 0.06 MILLION IRU/KG/DAY (5 MICROGRAMS/KG/DAY) BONE MARROW TRANSPLANTATION (BMT) - 0.11 MILLION IRU/KG/DAY (10 MICRO-GRAMS/KG/DAY) INTRAVENOUSLY: ADMINISTER INFUSION OVER 4-6 HOURS FOR A MAXIMUM OF 30 DAYS, BEGINNING THE DAY AFTER BMT.
CONTINUE UNTIL ABSOLUTE NEUTROPHIL COUNT (ANC) IS >= 100/MM(3)
AIDS-RELATED CMV RETINITIS - ADJUVANT THERAPY TO DHPG - 0.06 MILLION IRU/KG (5 MICROGRAMS/KG) SUBCUTANEOUSLY, ONCE DAILY. AFTER THE FIFTH LEUCOMAX DOSE HAS BEEN ADMINSITERED THE DOSE MAY BE TRITRATED TO MAINTAIN THE ANC AND WBC AT THE DESIRED LEVELS, USUALLY >= 20,0000/MM(3) RESPECITVELY.

4.3/4.9 Clinical particulars section

A) CONTRAINDICATIONS:
   LEUCOMAX IS CONTRAINDICATED IN PATIENTS WITH A HISTORY OF HYPER-SENSITIVITY TO MOLGRAMOSTIM OR ANY COMPONENT OF THE INJECTABLE FORMULATION. LEUCOMAX SHOULD NOT BE USED IN PATIENTS WITH MYELOID MALIGNANCIES.
B) INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION:
   DRUG/DRUG INTERACTIONS: SINCE DOSING WITH LEUCOMAX HAS BEEN ASSOCIATED WITH A DECREASE IN SERUM ALBUMIN, DRUGS THAT ARE HIGHLY BOUND TO SERUM ALBUMIN MAY REQUIRE DOSAGE ADJUSTMENT.

ALTHOUGH NO ADVERSE DRUG INTERACTION HAS BEEN REPORTED WITH LEUCOMAX, THE POSSIBILITY OF A DRUG-DRUG INTERACTION CANNOT BE EXCLUDED COMPLETELY.

C) EFFECTS ON ABILITY TO DRIVE AND TO USE MACHINES:
NONE

D) UNDESIRABLE EFFECTS:
SINCE MANY OF THE UNDESIRABLE EFFECTS REPORTED DURING LEUCOMAX CLINICAL TRIALS ARE OFTEN ASSOCIATED WITH UNDERLYING OR CONCURRENT DISEASES OR THEIR TREATMENT THE CAUSAL RELATIONSHIP OF THESE EFFECTS TO LEUCOMAX CANNOT BE DEFINITIVELY DETERMINED. MOST ADVERSE REACTIONS OBSERVED WERE MILD OR MODERATE IN SEVERITY. RARELY, THESE WERE SEVERE OR LIFE-THREATENING.
THE MOST FREQUENTLY REPORTE UNDESIRABLE EFFECTS ACROSS ALL INDICATIONS WERE FEVER, NAUSEA, DYSPNEA, DIARRHEA, RASH, RIGORS, INJECTION SITE REACTION (WITH SUBCUTANEOUS ADMINISTRATION), VOMITING, FATIGUE, ANOREXIA, MUSCULOSKELETAL PAIN AND ASTHENIA.
LESS FREQUENTLY REPORTED EVENTS INCLUDE: NONSPECIFIC CHEST PAIN, STOMATITIS, HEADACHE, INCREASED SWEATING, ABDOMINAL PAIN, PRURITUS, DIZZINESS, PERIPHERAL EDEMA, PARESTHESIA AND MYALGIA.
SERIOUS REACTIONS, WHICH OCCURED RARELY IN CLINICAL TRIALS, INCLUDE: ANAPHYLAXIS, BRONCHOSPASM, CARDIAC FAILURE, CAPILLARY LEAK SYNDROME, CEREBROVASCULAR DISORDERS, CONFUSION, CONVULSIONS, HYPOTENSION, CARDIAC RHYTHM ABNORMALITIES, INTRACRANIAL HYPERTENSION, PERICARDIAL EFFUSION, PERICARDITIS, PLEURAL EFFUSION, PULMONARY OEDEMA AND SYNCOPE.
LABORATORY FINDINGS:
IN ALL PATIENT GROUPS THE MOST FREQUENTLY OCCURING CHANGES IN LABORATORY VALUES WERE DECREASED PLATELET COUNT, DECREASED HAEMOGLOBIN LEVEL, DECREASED SERUM ALBUMIN LEVEL AND INCREASED EOSINOPHILS (ABSOLUTE COUNT AND PERCENT). THE CAUSAL RELATIONSHIP OF THESE CHANGES TO LEUCOMAX CANNOT BE DETERMINED DEFINITIVELY.
THE FREQUENCY OF ANTIBODIES THAT BIND TO MOLGRAMOSTIM, MEASURED BY ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA) AND BIOASSAY, WAS DETERMINED TO BE 1% POST-TREATMENT NO LOSS OF ACTIVITY OF LEUCOMAX WAS EVIDENT IN THESE PATIENTS.

E) USE DURING PREGNANCY AND LACTATION: SAFETY OF LEUCOMAX FOR USE IN HUMAN PREGNANCY HAS NOT BEEN ESTABLISHED. ANIMAL STUDIES HAS SHOWN REPRODUCTIVE TOXICITY. IN PRIMATE MODELS, ADMINISTRATION OF MOLGRAMOSTIN WAS ASSOCIATED WITH FOETAL DEATH AND SPONTANEIOUS ABORTION AT DOSES OF 0.07 AND 0.11 MILLION IRU/KG/DAY (6 AND 10 MICROGRAMS/KG/DAY).
IN THE ABSENCE OF CLINICAL DATA IN PREGNANCY, THE THERAPEUTIC BENEFIT TO THE PATIENT MUST BE WEIGHED AGAINST POTENTIAL RISKS TO THE PROGRESS OF THE PREGNANCY
NURSING MOTHERS - IT IS NOT KNOWN WHETHERR LEUCOMAX IS EXCRETED IN HUMAN MILK. HOWEVER, BECAUSE OF THE POTENTIAL FOR ADVERSE EFFECTS IN INFANTS, NURSING IS NOT RECOMMENDED IN WOMEN RECEIVING LEUCOMAX.
EFFECTS ON FERTILITY: STUDIES TO DETERMINE THE EFFECTS OF LEUCOMAX ON FERTILITY HAVE NOT BEEN CARRIED OUT IN HUMAN SUBJECTS.

F) SPECIAL PRECAUTIONS FOR USE:
LEUCOMAX SHOULD BE USED UNDER THE SUPERVISION OF A PHYSICIAN EXPERIENCED IN THE TREATMENT OF ONCOLOGIC AND HEMATOIETIC DISORDERS OR INFECTIOUS DISEASES.
THE FIRST DOSE OF LEUCOMAX SHOULD BE ADMINISTERD UNDER MEDICAL SUPERVISION.
ACUTE, SEVERE, LIFE-THREATENING HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS ANGIOEDEMA OR BRONCHOCONSTRICTION HAVE OCCURRED IN PATIENTS RECEIVING LEUCOMAX.IF SUCH REACTIONS OCCUR, LEUCOMAX SHOULD BE WITHDRAWN IMMEDIATELY AND NOT REINTRODUCED.
IN CLINICAL STUDIES, LEUCOMAX HAS BEEN ASSOCIATED INFREQUENTLY WITH PLEURITIS OR PLEURAL EFFUSION. PERICARDITIS OCCURED IN 2% (21/1098)

AND PERICARDIAL EFFUSION IN <2% (16/1098). IF SUCH REACTIONS OCCUR, LEUCOMAX SHOULD BE WITHDRAWN.
PATIENTS WITH PRE-EXISTING PULMONARY DISEASE MAY BE PREDISPOSED TO DECREASED PULMONARY FUNCTION AND DYSPNEA, AND SHOULD BE MONITORED CLOSELY WHEN BEING TREATED WITH LEUCOMAX.
IN CLINICAL TRIALS, ADVERSE EVENTS REPORTED WITH INITIATION OF DOSING WERE MOSTLY MILD TO MODERATE IN SEVERITY, AND INCLUDED RIGORS, DYSPNEA, FEVER, NAUSEA, VOMITING, NONSPECIFIC CHEST PAIN, ASTHENIA, HYPOTENSION OR FLUSHING. FOR FURTHER INFORMATION PLEASE SEE GOLD FILE

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR IS A MULTI-LINEAGE GLYCOPROTEIN REGULATOR INVOLVED IN BOTH THE REGULATION OF HAEMATOPOIESIS AND THE ACTIVATION OF MATURE MYELOID CELLS. IN VITRO THE RECOMBINANT HUMAN GM-CSF, MOLGRAMOSTIM, STIMULATES THE PROLIFERATION AND DIFFERENT-ION OF HAEMATOPOIETIC PRECURSOR CELLS THAT RESULT IN THE PRODUCTION OF GRANULOCYTES, MONOCYTES/MACROPHAGES AND T-LYMPHOCYTES.
STUDIES ON FRESH TUMOUR EXPLANTS IN THE HUMAN TUMOUR CLONOGENIC ASSAY HAVE DEMONSTRATED THAT MOLGRAMOSTIM NEITHER STIMULATES NOR INHIBITS TUMOUR CELL GROWTH. RHUG-CSF CAN EXHANCE EXPRESSION OF MAJOR HISTO-COMPATIBILITY CLASS II ANTIGENS ON HUMAN MONOCYTES AND CAN AUGMENT FUNCTIONAL ACTIVITY OF MATURE NEUTROPHILS, INCLUDING ENHANCED PHAGOCY-TOSIS OF BACTERIA, ENHANCED CYTOXICITY TOWARD MALIGNANT CELLS AND PRIM-ING OF NEUTROPHILS FOR ENHANCED OXIDATIVE METABOLISM, AN IMPORTANT REACTION RELATED TO HOST DEFENCE.
INTRAVENOUS OR SUBCUTANEOUS BOLUS ADMINISTRATION OF MOLGRAMOSTIM TO CYMOMOLGUS MONKEYS RESULTS IN SIGNIFICANT INCREASES IN THE CIRCULATING WHITE BLOOD CELL (WBC) COUNT. SERIAL DIFFERENTIAL COUNTS INDICATE THAT THIS INCREASE IS DUE MAINTLY TO NEUTROPHILIC GRANULOCYTES AND SECOND-ARILY, TO LYMPHOCYTES AND EOSINOPHILS. FOR FURTHER INFORMATION PLEASE SEE GOLD FILE.

5.2 Pharmacokinetic properties

STUDIES IN RATS SHOWED THAT RADIOACTIVITY WAS EXTENSIVELY DISTRIBUTED FOLLOWING INTRAVENOUS ADMINISTRATION OF 125 I-RHUGM-CSF. THE DRUG APPEARED TO BE RAPIDLY METABOLISED AND EXCRETED. THE PHARMACOKNETIC PROFILES OF MOLGRAMOSTIN WERE SIMILAR IN MONKEYS, HEALTHY MALE VOLUNT-EERS AND PATIENTS. AFTER SUBCUTANEOUS DOSES OF 0.03, 0.11 OR 0.22 MILLION IRU-KG (3, 10 OR 20 MICROGRAMS/KG) AND FOLLOWING INTRAVENOUS DOSES OF 0.03 TO 0.33 IRU/KG (3 TO 30 MICROGRAMS/KG) INCREASES IN THE TOTAL AREA UNDER THE CURVE (AUC) WERE DOSE RELATED. MAXIMUM MOLGRAMOSTIN SERUM CONCENTRATIONS WERE REACHED WITHIN THREE TO FOUR HOURS AFTER SUBCUTANEOUS ADMINISTRATION. MOLGRAMOSTIM HAD AN ELIMINATION HALF-LIFE OF ONE TO TWO HOURS FOLLOWING INTRAVENOUS ADMINISTRATION AND TWO TO THREE HOURS FOLLOWING SUBCUTANEOUS ADMINISTRATION. THE SLIGHTLY LONGER HALF-LIFE OBSERVED AFTER SUBCUTANEOUS ADMINISTRATION IS PROBABLY DUE TO PROLONGED ABSORPTION FROM THE INJECTIN SITE.

PHARMACEUTICAL PROPERTIES

6.1 List of excipients

NORSK - NO DATA

6.2 Incompatibilites

NORSK - NO DATA

6.3 Shelf life

NORSK - NO DATA

6.4 Special precautions for storage

NORSK - NO DATA

6.5 Nature and contents of container

NORSK - NO DATA

6.6 Instructions for use/handling

NORSK - NO DATA

ADMINISTRATION DETAILS

7. Marketing authorization holder

NORSK - NO DATA

8. Marketing Authorization number

NORSK - NO DATA

9. Date of first authorization/renewal of authorization

NORSK - NO DATA

10. Date of (partial) revision of the text

NORSK - NO DATA