criteria. It was concluded that in this study none of the patients showed anti-peg GCSF antibody development against pegfilgrastim.

OVERDOSE
Single subcutaneous doses of 300 mcg/kg have been administered to healthy volunteers and patients with non-small cell lung cancer without serious adverse effects. These patients experienced a mean maximum ANC of 55 x 10^9/L, with a corresponding mean maximum WBC of 67 x 10^9/L. The absolute maximum ANC observed was 96 x 10^9/L wit a corresponding absolute maximum WBC observed of 120 x 10^9/L. The duration of leukocytosis ranged from 6 to 13 days. Leukopheresis should be considered in the management of symptomatic individuals.

INCOMPATIBILITIES
This medicinal product must not be mixed with other medicinal products, particularly with sodium chloride solutions. (Normal Saline 0.9% NaCl or half saline or 5% DNS- Dextrose Normal Saline)

SHELF LIFE: 24 Months

PACKING INFORMATION
Pegkine is supplied in a 0.6 mL single dose prefilled syringe containing 6 mg Pegfilgrastim. Each prefilled syringe is placed in a plastic trough and packed in a carton along with a package insert.

STORAGE AND HANDLING INSTRUCTION
Store refrigerated between 2 °C to 8 °C (36 °F to 46 °F) in the carton to protected from light. Do not shake. The preparation should not be allowed to freeze. Keep out of reach and sight of children.

Manufactured by:
Intas Pharmaceuticals Ltd.
Plot No. 423/P/A, Sarkhej - Bavla Highway,
Village - Moraiya, Taluka - Sanand,
District - Ahmedabad-382 213, Gujarat, INDIA.

Marketing Authorization holder:
Accord Healthcare Ltd.
Saga House, 319, Pinner Road,
North Harrow, Middlesex, HA1 4HF, UK.

AW-QA-1727-01

For the use of an Oncologist or Hospital only

PEG Kine

PFS 6 mg / 0.6 mL

Pegfilgrastim Injection PFS 6 mg
Pegylated r-Human Granulocyte Colony Stimulating Factor (rHu GCSF) Injection 6 mg

DECSRIPTION AND COMPOSITION
Pegfilgrastim is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Filgrastim is a water soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons. Filgrastim is obtained from the bacterial fermentation of a strain of Escherichia coli transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim, a 20 kDa monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of filgrastim. The average molecular weight of pegfilgrastim is approximately 39 kDa.

Each 0.6 mL of prefilled syringe contains: 6 mg of Pegylated Recombinant Human G-CSF

Each Syringe contains 6 mg Pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution. The pH of the solution is 4.0

Contents	Pegkine 6 mg/0.6 mL
Pegfilgrastim drug substance	6 mg
Glacial Acetic Acid	0.35 mg
Sorbitol	30.0 mg
Polysorbate 20	0.024 mg
Sodium Hydroxide	0.034 mg
Water for injection (*qs*)	0.6 mL

DOSAGE FORM
Solution for Injection (6 mg per 0.6 mL in single use prefilled syringe)

PRECLINICAL PHARMACOLOGY
The relative potency of Pegfilgrastim was assessed in an in-vivo bioassay using neutropenic mice, and compared with the reference standard. In this test both the test and reference drug were found comparable and equipotent. Pharmacokinetic studies were done in non-neutropenic rat and compared with the reference standard. The half-lives of the product were comparable to that of the reference standard.

Acute toxicity studies were conducted in rats and mice by administering i.v. and s.c. single doses of 1000, 5000 and 10000 mcg/Kg of Pegfilgrastim. The animals were observed for mortality, clinical signs and gross organ examinations. There was no death or any other adverse effect in the animals at all the dose levels. In repeat dose sub acute toxicity studies in rats, mice and rabbits a dose of 100, 500 and 1000 mcg/Kg was administered for a period of 28 days by s.c. and i.v. routes. The animals were examined for body weight changes, food consumption, blood chemistry and histopathological examination of body organs. There was no abnormality detected in any of the parameters in the animals. Pegfilgrastim was well tolerated in low, medium and high dose levels.

CLINICAL PHARMACOKINETIC PROPERTIES
The pharmacokinetics of pegfilgrastim is nonlinear in cancer patients and clearance decreases with increase in the doses. Neutrophil receptor binding is an important component of the clearance of pegfilgrastim and serum clearance is directly related to the number of neutrophils. The concentration of pegfilgrastim declines rapidly at the onset of neutrophil recovery that follows myelosuppression chemotherapy. Additionally, patients with higher body weights experience higher systemic exposure of pegfilgrastim after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of pegfilgrastim has been observed in cancer patients. The half life of pegfilgrastim ranges from 15 to 80 hours after subcutaneous injection.

CLINICAL PHARMACODYANAMIC PROPERTIES
Pegfilgrastim is a pegylated recombinant human granulocyte colony stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptor thereby stimulating proliferation, differentiation, commitment and end cell function activation. Studies on cellular proliferation, receptor binding and neutrophil function demonstrate that pegfilgrastim has mechanism of action similar to its patent drug filgrastim. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo as compared to filgrastim.

INDICATIONS
Pegfilgrastim is indicated to decrease the incidence of infection, as

manifested by febrile neutropenia, in patients with non myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

DOSE AND METHOD OF ADMINISTRATION

The recommended dosage of pegfilgrastim is a single subcutaneous injection of 6 mg administered by subcutaneous route once per chemotherapy cycle. Pegfilgrastim should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy. The 6 mg fixed-dose formulation should not be used in infants, children and smaller adolescents weighing less than 45 kg. No dosing adjustment is necessary for renal dysfunction. Pegfilgrastim should be visually inspected for discoloration and particulate matter and if found, should not be administered.

CONTRAINDICATIONS

Do not administer pegfilgrastim to patients with a history of serious allergic reaction to pegfilgrastim or filgrastim or patients with known history of E Coli derived proteins.

WARNINGS

General

The safety and efficacy of pegfilgrastim for peripheral blood progenitor cell (PBPC) mobilization has not been evaluated. Pegfilgrastim should not be used for PBPC mobilization.

Splenic Rupture

Splenic rupture, including fatal cases, has been reported following the administration of pegfilgrastim and its parent compound, filgrastim. Patients receiving pegfilgrastim who report left upper abdominal and / or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Acute Respiratory Distress Syndrome (ARDS)

Acute Respiratory Distress Syndrome (ARDS) has been reported in patients receiving pegfilgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving pegfilgrastim who develop fever, lung infiltrates or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, pegfilgrastim should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

Allergic reaction

Allergic reactions to pegfilgrastim, including anaphylaxis, skin rash and urticaria have been reported in post marketing experience. If a serious allergic reaction occurs, appropriate therapy should be administered with close patient follow-up over several days. Pegfilgrastim should be permanently discontinued in patients with serious allergic reaction.

Sickle Cell Disease

Severe sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease. Severe sickle cell crises, in some cases resulting in death, have also been associated with filgrastim, the parent compound of pegfilgrastim. Only physician qualified by specialized training or experience in the treatment of patients with sickle cell disorders should prescribe Pegfilgrastim should be used with caution in patients with sickle cell disease, and only after careful consideration of the potential risks and benefits.

PRECAUTIONS

Use with chemotherapy and / or radiation therapy

Pegfilgrastim should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy because of the potential for an increase in sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy. The use of pegfilgrastim has not been studied in patients receiving chemotherapy associated with delayed myelosuppression (e.g. Nitrosourea, Mitomycin C). The administration of pegfilgrastim concomitantly with 5-fluorouracil or other antimetabolites has not been evaluated in patients. Administration of pegfilgrastim at 0, 1 and 3 days before 5-fluorouracil results in increased mortality in mice: administration of pegfilgrastim 24 hours after 5-fluorouracil did not adversely affect survival. The use of pegfilgrastim has not been studied in patients receiving radiation therapy.

Potential for tumour growth stimulating effects on malignant cells

The granulocyte colony stimulating factor (G-CSF) receptor through which pegfilgrastim and filgrastim act has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia,

disease for which pegfilgrastim is not approved, cannot be excluded.

Laboratory Monitoring

To assess the patient's hematologic status and ability to tolerate Myelosuppressive chemotherapy, a complete blood count and platelet count should be obtained before chemotherapy is administered. Regular monitoring of hematocrit value and platelet count is recommended.

Carcinogenesis, Mutagenesis & Impairment of Fertility

No mutagenesis studies were conducted with pegfilgrastim. The carcinogenic potential of pegfilgrastim has not been evaluated in long-term animal studies. In toxicity studies of 6 months duration in rats given once weekly subcutaneous injections of upto 1000 mcg/Kg of pegfilgrastim, no precancerous or cancerous lesions were noted. When administered once weekly via subcutaneous injections to male and female rats at dose upto 1000 mcg/Kg prior to, during mating, reproductive performance, fertility and sperm assessment parameters were not affected.

USE IN SPECIAL POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant woman. Pegfilgrastim should be used during pregnancy only if potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

It is not know whether pegfilgrastim is secreted in human milk. Caution should be exercised when administered to a nursing woman.

Pediatric Use

Safety and effectiveness of pegfilgrastim in pediatric patients have not been established. The 6 mg fixed-dose formulation should not be used in infants, children and smaller adolescents weighing less than 45 kg.

Geriatric Use

No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

Renal Impairment

Pegfilgrastim dose adjustment in patients with renal dysfunction is not necessary.

DRUG INTERACTIONS

No formal drug interaction studies between pegfilgrastim and other drugs have been performed. Drugs such as lithium may potentiate the release of neutrophils; patients receiving pegfilgrastim and lithium should have more frequent monitoring of neutrophil counts. Increased hematopoietic activity of the bone marrow in reponse to growth factor therapy may result in transient positive bone-imaging changes. Consider these finding when interpreting bone-imaging results.

UNDESIRABLE EFFECTS

The most common adverse reactions that are bone pain and pain in extremity were reported more in patients treated with pegfilgrastim as compared to placebo treated patients. The other common undesirable effects includes vomiting, headache, anemia, constipation, fatigue, diarrhea, general weakness, mucositis, neutropenia, fever, body pain, taste alteration, alopecia, anorexia, skeletal pain, asthenia, pyrexia, dyspepsia, myalgias, insomnia, abdominal pain, arthralgias, peripheral edema, dizziness, granulocytopenia, stomatitis and neutropenic fever. Leukocytosis (WBC counts > 100 X 10^9/L) is observed in less than 1% of patients with non-myeloid malignancies receiving pegfilgrastim. Leukocytosis is not associated with any adverse effects.

Immunogenicity

The incidence of antibody development in patients receiving pegfilgrastim has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim of pegfilgrastim, the nature and specificity of these antibodies has not been adequately studied.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against pegfilgrastim may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia, but this has not been observed in clinical studies of pegfilgrastim.

The experimental data obtained from post marketing surveillance study showed that none of the patients were observed to develop any immunogenic response according to the specified screening cut point