# PROFESSIONAL INFORMATION

## SCHEDULING STATUS

**S4**

## 1 NAME OF THE MEDICINE

**STROPEG** 6 mg/0,6 ml solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 6 mg of pegfilgrastim in 0,6 ml solution for injection. Pegfilgrastim is composed of filgrastim (recombinant methionyl human granulocyte colony stimulating factor (G-CSF)) with a 20 kDa polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue. Filgrastim is produced in *Escherichia coli* cells by recombinant DNA technology.

Contains sugar: D-sorbitol 30 mg per pre-filled syringe.

For full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution free from visible particles.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

To reduce the duration of neutropenia and the incidence of febrile neutropenia and the incidence of infection as manifested by febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

## 4.2 Posology and method of administration

**Posology**

STROPEG therapy should be initiated and supervised by medical practitioners experienced in oncology and/or haematology.

***Adults (≥ 18 years)***

One 6 mg dose (a single pre-filled syringe) of STROPEG is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy.

***Children and Adolescents:***

There are insufficient data to recommend the use of STROPEG in children and adolescents under 18 years of age.

**Method of administration**

STROPEG pre-filled syringe is for single use only.

STROPEG is a sterile but unpreserved solution.

Before administration, STROPEG solution should be inspected for visible particles.

Only a solution that is clear and colourless should be injected.

Excessive shaking may aggregate pegfilgrastim, rendering it biologically inactive.

Allow the pre-filled syringe to reach room temperature before injecting.

## 4.3 Contraindications

- Hypersensitivity to pegfilgrastim, filgrastim, *E. coli* derived proteins, or to any of the excipients (see section 6.1).

## 4.4 Special warnings and precautions for use

The safety and efficacy of STROPEG in patients with acute leukaemia have not been sufficiently investigated to enable treatment recommendations.

Granulocyte-colony stimulating factor can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

The safety and efficacy of STROPEG have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukaemia, and in patients with secondary AML; therefore, it should not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from AML.

The safety and efficacy of STROPEG administration in *de novo* AML patients aged < 55 years with cytogenetics t (15;17) have not been established.

The safety and efficacy of STROPEG have not been investigated in patients receiving high dose chemotherapy.

STROPEG should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

STROPEG injection must not be mixed with other medicines, particularly with sodium chloride solutions (refer to section 6.2).

***Pulmonary adverse events***

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk (see Section 4.8).

The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS). In such circumstances STROPEG should be discontinued at the discretion of the medical practitioner and the appropriate treatment given (see section 4.8).

***Glomerulonephritis***

Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

***Capillary leak syndrome***

Capillary leak syndrome has been reported after granulocyte-colony stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care (see Section 4.8).

***Splenomegaly and splenic rupture***

Generally asymptomatic cases of splenomegaly and cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim (see section 4.8). Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

***Thrombocytopenia and anaemia***

Treatment with STROPEG alone does not preclude thrombocytopenia and anaemia because full dose myelosuppressive chemotherapy is maintained on the prescribed schedule. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic medicines which are known to cause severe thrombocytopenia.

***Sickle cell anaemia***

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease (see section 4.8). Therefore, medical practitioners should use caution when prescribing STROPEG in patients with sickle cell trait or sickle cell disease, should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis.

***Leukocytosis***

White blood cell (WBC) counts of 100 x $10^9$/L or greater have been observed in less than 1 % of patients receiving pegfilgrastim (as in STROPEG). No adverse events directly attributable to this degree of leukocytosis have been reported. Such elevation in white blood cells is transient, typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of this medicine. Consistent with the clinical effects and the potential for leukocytosis, a WBC count should be performed at regular intervals during therapy. If leukocyte counts exceed 50 x $10^9$/L after the expected nadir, this medicine should be discontinued immediately.

***Hypersensitivity***

Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with pegfilgrastim. Permanently discontinue STROPEG in patients with clinically significant hypersensitivity. Do not administer STROPEG to patients with a history of hypersensitivity to pegfilgrastim or filgrastim. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days.

***Stevens-Johnson syndrome***

Stevens-Johnson syndrome (SJS), which can be life-threatening or fatal, has been reported rarely in association with pegfilgrastim treatment. If the patient has developed SJS with the use of STROPEG, treatment with STROPEG must not be restarted in this patient at any time.

***Immunogenicity***

As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against pegfilgrastim is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

***Aortitis***

Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. c-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of GCSF. See also section 4.8.

***Other warnings***

The safety and efficacy of STROPEG for the mobilisation of blood progenitor cells in patients or healthy donors has not been adequately evaluated.

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging findings. This should be considered when interpreting bone-imaging results.

***Excipient warning***

Contains D-sorbitol and may have a laxative effect. Patients with the rare hereditary condition of sorbitol/maltitol/ lactitol intolerance should not use STROPEG.

## 4.5 Interaction with other medicines and other forms of interaction

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, STROPEG should be administered at least 24 hours after administration of cytotoxic chemotherapy. In clinical trials, pegfilgrastim has been safely administered 14 days before chemotherapy. Concomitant use of STROPEG with any chemotherapy medicine has not been evaluated in patients. In animal models concomitant administration of STROPEG and 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression.

Possible interactions with other haematopoietic growth factors and cytokines have not been specifically investigated in clinical trials.

The potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be harmful.

The safety and efficacy of STROPEG have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression e.g., nitrosoureas.

Specific interaction or metabolism studies have not been performed however clinical trials have not indicated an interaction of pegfilgrastim with any other medicines.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

Safety in pregnancy has not been established. Studies in animals have shown reproductive toxicity. The potential risk to the human embryo or foetus is unknown.

STROPEG should not be used during pregnancy.

### Breastfeeding

STROPEG should not be administered to women who are breastfeeding.

### Fertility

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

## 4.7 Effects on ability to drive and use machines

STROPEG has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

### a. Summary of the safety profile

The most frequently reported adverse reactions were bone pain and musculoskeletal pain. Bone pain was generally of mild to moderate severity, transient and could be controlled in most patients with standard analgesics.

Hypersensitivity-type reactions, including skin rash, urticaria, angioedema, dyspnoea, erythaema, flushing, and hypotension occurred on initial or subsequent treatment with pegfilgrastim (less frequent).

Serious allergic reactions, including anaphylaxis can occur in patients receiving pegfilgrastim (less frequent) (see section 4.4).

Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported as less frequent in cancer patients undergoing chemotherapy following administration of granulocyte-colony stimulating factors; see section 4.4 and section “Description of selected adverse reactions” below.

Splenomegaly, generally asymptomatic, is less frequent.

Splenic rupture including some fatal cases is less frequently reported following administration of pegfilgrastim (see section 4.4).

Less frequently pulmonary adverse reactions including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis have been reported. Less frequent, cases have resulted in respiratory failure or ARDS, which may be fatal (see section 4.4).

Isolated cases of sickle cell crises have been reported in patients with sickle cell trait or sickle cell disease (less frequent in sickle cell patients) (see section 4.4).

### b. Tabulated summary of adverse reactions

The data in the table below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequency of adverse reactions listed below is defined using the following convention: frequent; less

frequent or frequency unknown (cannot be estimated from the available data).

| **MedDRA system organ class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| Blood and lymphatic system disorders | Frequent | Thrombocytopenia*, leukocytosis* |
| | Less frequent | Sickle cell crisis**, splenomegaly**, splenic rupture** |
| Immune system disorders | Less frequent | Hypersensitivity reactions, anaphylaxis |
| Metabolism and nutrition disorders | Less frequent | Elevations in uric acid |
| Nervous system disorders | Frequent | Headache* |
| Vascular disorders | Less frequent | Capillary leak syndrome*, aortitis |
| Respiratory, thoracic and mediastinal disorders | Less frequent | Acute Respiratory Distress Syndrome**,pulmonary adverse reactions (interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis), haemoptysis, pulmonary haemorrhage |
| Gastrointestinal disorders | Frequent | Nausea* |
| Skin and subcutaneous tissue disorders | Frequent | Dermatitis contact* |
| | Less frequent | Sweet's syndrome (acute febrile dermatosis)*, **, cutaneous vasculitis*, **, Stevens-Johnson |

| MedDRA system organ class | Frequency | Adverse reactions |
|---|---|---|
| | | syndrome |
| Musculoskeletal and connective tissue disorders | Frequent | Bone pain, musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, musculoskeletal pain, neck pain) |
| Renal and urinary disorders | Less frequent | Glomerulonephritis** |
| General disorders and administration site conditions | Frequent | Injection site pain*, application site reactions*, non-cardiac chest pain |
| Investigations | Less frequent | Elevations in lactate dehydrogenase and alkaline, phosphatase*, transient elevations in LFTs for ALT or AST* |

* See section “Description of selected adverse reactions” below.

** This adverse reaction was identified through post-marketing surveillance but not observed in randomised, controlled clinical trials in adults. The frequency category was estimated from a statistical calculation based upon 1,576 patients receiving pegfilgrastim in nine randomised clinical trials.

**c. Description of selected adverse reactions**

Less frequent cases of Sweet's syndrome have been reported, although in some cases underlying haematological malignancies may play a role.

Less frequent events of cutaneous vasculitis have been reported in patients treated with pegfilgrastim. The mechanism of vasculitis in patients receiving pegfilgrastim is unknown.

Injection site reactions, including injection site erythaema (less frequent) as well as injection site pain (frequent) have occurred on initial or subsequent treatment with pegfilgrastim.

Frequent cases of leukocytosis (White Blood Count [WBC] > 100 x $10^9$/L) have been reported (see section 4.4).

Reversible, mild to moderate elevations in uric acid and alkaline phosphatase, with no associated clinical effects, were uncommon; reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, were uncommon in patients receiving Neulasta following cytotoxic chemotherapy.

Nausea and headaches were frequently observed in patients receiving chemotherapy.

Less frequent elevations in liver function tests (LFTs) for alanine aminotransferase (ALT) or aspartate aminotransferase (AST), have been observed in patients after receiving pegfilgrastim following cytotoxic chemotherapy. These elevations are transient and return to baseline.

Frequent cases of thrombocytopenia have been reported.

Cases of capillary leak syndrome have been reported in the post-marketing setting with granulocyte-colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4).

**d. Paediatric population**

The experience in children is limited. A higher frequency of serious adverse reactions in younger children aged 0 - 5 years (92 %) has been observed

compared to older children aged 6 - 11 and 12 - 21 years respectively (80 % and 67 %) and adults. The most frequent adverse reaction reported was bone pain.

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

### 4.9 Overdose

Single doses of 300 µg/kg have been administered to a limited number of healthy volunteers and patients with non-small cell lung cancer without serious adverse effects. The adverse events were similar to those in subjects receiving lower doses of pegfilgrastim.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunostimulants, colony stimulating factor; ATC Code: L03AA13

Pharmacological classification: A 8.5 Medicines acting on blood and haemopoietic system – others

Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kDa polyethylene glycol (PEG) molecule. Pegfilgrastim is a

sustained duration form of filgrastim due to decreased renal clearance. A transient increase in the white cell count is the expected consequence of pegfilgrastim administration. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. Neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. G-CSF has shown *in vitro* stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells *in vitro*, and similar effects may be seen on some non-myeloid cells *in vitro*.

## 5.2 Pharmacokinetic properties

**Absorption**

After a single subcutaneous dose of pegfilgrastim, the peak serum concentration of pegfilgrastim occurs at 16 to 120 hours after dosing.

**Distribution**

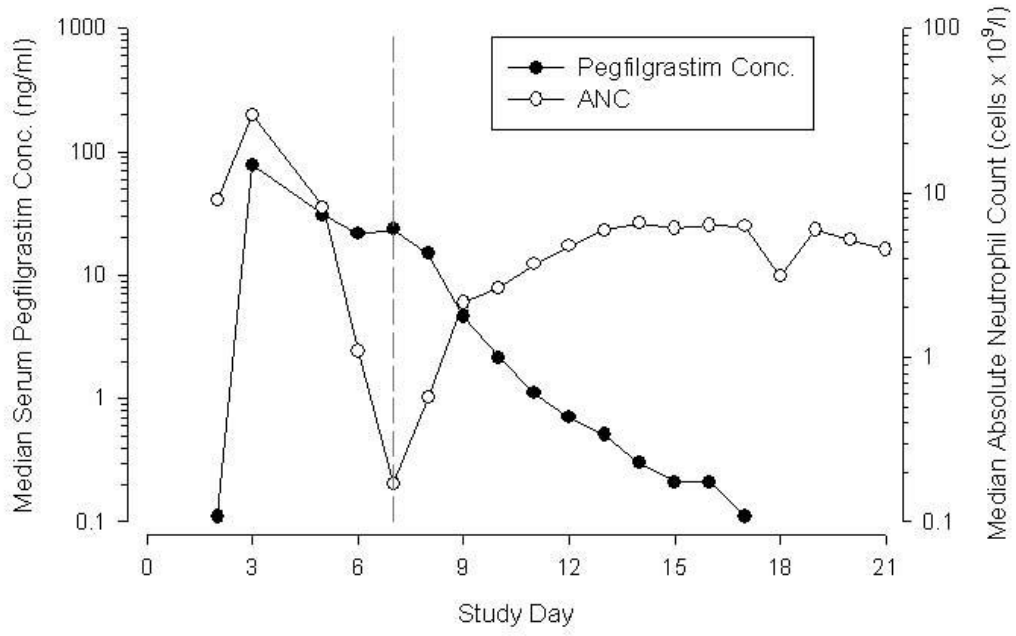
Serum concentrations of pegfilgrastim are maintained during the period of neutropenia after myelosuppressive chemotherapy. The distribution of pegfilgrastim was limited to the plasma compartment.

**Elimination**

The elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance (> 99 %), which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declines rapidly at the onset of neutrophil recovery (see Figure 1).

***Figure 1: Profile of median pegfilgrastim serum concentration and Absolute Neutrophil Count (ANC) in chemotherapy-treated patients after a single 6 mg***

***injection***




**Pharmacokinetics in Special Populations**

Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment. Limited data indicate that the pharmacokinetics of pegfilgrastim in elderly subjects (> 65 years) is similar to that in adults.

**Paediatric population**

The pharmacokinetics of pegfilgrastim were studied in 37 paediatric patients with sarcoma. The systemic exposure (AUC0-inf, mean ± Standard Deviation) of pegfilgrastim after subcutaneous administration at 100 µg/kg was 22,0 (± 13,1) µg·hr/ml in the 6-11 years age group (n = 10), 29,3 (± 23,2) µg·hr/ml in the 12-21 years age group (n = 13) and 47,9 (± 22,5) µg·hr/ml in the youngest age group (0-5 years, n = 11). The terminal elimination half-lives of the corresponding age groups were 20,2 (± 11,3) hours, 21,2 (± 16,0) hours and 30,1 (± 38,2) hours, respectively. Note that the systemic exposure is much higher and the T1/2, longer in children aged 0 - 6 years. See Sections 4.2 and 4.4.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sorbitol (E420)

Glacial acetic acid

Polysorbate 20

Sodium hydroxide

Water for injection

## 6.2 Incompatibilities

STROPEG injection must not be mixed with other medicines, particularly with sodium chloride solutions (refer to section 4.4).

## 6.3 Shelf life

36 months.

## 6.4 Special precautions for storage

Store at 2 – 8 ˚C (in a refrigerator).

Do not freeze or shake.

Keep the container in the outer carton in order to protect from light.

Accidental exposure to freezing temperatures for a single period of less than 48 hours does not adversely affect the stability of STROPEG.

STROPEG may be exposed to room temperature (not above 30 ˚C) for a maximum single period of up to 72 hours. STROPEG left at room temperature for more than 72 hours should be discarded.

## 6.5 Nature and contents of container

1 ml clear colourless Type I glass pre-filled syringe (containing 6 mg/0,6 ml) with

a stainless-steel needle, for single use only. Cartons contain one single-use, pre-filled syringe along with a patient information leaflet.

### 6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

**Kahma Biotech (Pty) Ltd**

106, 16th Road

Midrand

## 8 REGISTRATION NUMBER

560108

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 April 2023

## 10 DATE OF REVISION OF THE TEXT