SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FILGRASTIM TEVA 30, 30 MIU/0,5 mL, Solution for injection or infusion

FILGRASTIM TEVA 48, 48 MIU/0,8 mL, Solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection or infusion contains 60 million international units [MIU] (600 µg) of filgrastim.

FILGRASTIM TEVA 30: Each pre-filled syringe contains 30 MIU (300 µg) of filgrastim in 0,5 mL solution for injection or infusion.

FILGRASTIM TEVA 48: Each pre-filled syringe contains 48 MIU (480 µg) of filgrastim in 0,8 mL solution for injection or infusion.

Contains sugar (Each mL of solution contains 50 mg of sorbitol).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion

FILGRASTIM TEVA is a clear colourless solution, practically free from particles.

Diluted solution: Clear, colourless solution free from visible particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Established cytotoxic chemotherapy

FILGRASTIM TEVA is indicated for the reduction in the duration of neutropenia in patients on chemotherapy, except in patients with chronic myeloid leukaemia and myelodysplastic syndromes.

4.2 Posology and method of administration

Posology

FILGRASTIM TEVA therapy should only be given in collaboration with an oncology centre which has experience in granulocyte-colony stimulating factor.

(G-CSF) treatment and haematology and has the necessary diagnostic facilities.

Established cytotoxic chemotherapy:

The recommended dose of FILGRASTIM TEVA is 0,5 MIU (5 µg)/kg/day.

The first dose of FILGRASTIM TEVA should not be administered less than 24 hours following cytotoxic chemotherapy.

Daily dosing with FILGRASTIM TEVA should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range.

Following established chemotherapy for solid tumours, lymphomas and lymphoid leukaemias, it is expected that the duration of treatment required to fulfil these criteria will be up to 14 days.

Following induction and consolidation treatment for acute myeloid leukaemia, the duration of treatment may be substantially longer (up to 38 days) depending on the type, dose and schedule of cytotoxic chemotherapy used.

In patients receiving cytotoxic chemotherapy, a transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of FILGRASTIM TEVA therapy. However, for a sustained therapeutic response,

FILGRASTIM TEVA therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of FILGRASTIM TEVA therapy prior to the time of the expected neutrophil nadir is not recommended.

Special populations

Elderly patients:

Clinical trials with FILGRASTIM TEVA have included a small number of elderly patients but special studies have not been performed in this group and therefore specific dosage recommendations cannot be made.

Paediatric population

Data from clinical studies in paediatric patients indicate that the safety and efficacy of FILGRASTIM TEVA are similar in both adults and children receiving cytotoxic chemotherapy.

Method of administration

FILGRASTIM TEVA may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5 % glucose solution, given over 30 minutes (refer to Instructions for dilution, section 6.6) The subcutaneous route is preferred in most cases.

4.3 Contraindications

- FILGRASTIM TEVA should not be administered to:
  - Patients with known hypersensitivity to filgrastim or any of the excipients listed in section 6.1.
  - Patients with chronic myeloid leukaemia and myelodysplastic syndromes.
  - Patients with severe congenital neutropenia (Kostmann's syndrome) with abnormal cytogenics.
- To increase the dose of cytotoxic chemotherapy beyond established dosage regimens.
- FILGRASTIM TEVA should not be used in patients with impaired renal or hepatic function.

- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

- **Sickle cell crisis** (see section 4.8)**:**

Sickle cell crisis, in some cases fatal, have been reported with the use of FILGRASTIM TEVA in patients with sickle cell trait or sickle cell disease. Physicians should exercise caution when considering the use of FILGRASTIM TEVA in patients with sickle cell trait or disease, and only initiate treatment after careful evaluation of the potential risks and benefits.

- **Malignant cell growth:**

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

The safety and efficacy of FILGRASTIM TEVA administration in patients with myelodysplastic syndrome or chronic myelogenous leukaemia has not been established. FILGRASTIM TEVA is not indicated for use in these conditions (see section 4.3). Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia (AML).

In view of limited safety and efficacy data in patients with secondary acute myeloid leukaemia, FILGRASTIM TEVA should be administered with caution. The safety and efficacy of FILGRASTIM TEVA administration in *de novo* AML patients aged < 55 years with good cytogenetics [t(8;21), t(15;17), and inv(16)] have not been established.

- **Osteopenia:**

Monitoring of bone density may be indicated in patients with underlying osteoporotic bone disease who undergo continuous therapy with FILGRASTIM TEVA for more than 6 months. Of note, increased

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

- **Interstitial pneumonia:**

Rare pulmonary undesirable effects, in particular interstitial pneumonia, have been reported after FILGRASTIM TEVA administration. Patients with recent history of pulmonary infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs, such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of Adult Respiratory Distress Syndrome (ARDs). FILGRASTIM TEVA should be discontinued and appropriate treatment given (See section 4.8).

- **Leucocytosis:**

FILGRASTIM TEVA can cause severe leucocytosis.

In view of the potential risks associated with severe leucocytosis, the white blood cell count should be performed at regular intervals during FILGRASTIM TEVA therapy. If leucocyte counts exceed 50 x 10^9/L after the expected nadir, FILGRASTIM TEVA should be discontinued immediately.

- **Pre-existing bone marrow suppression:**

The effects of FILGRASTIM TEVA in patients with substantially reduced myeloid progenitors have not been studied. FILGRASTIM TEVA acts primarily on neutrophil precursors to exert its effect in elevating neutrophil counts. Therefore, in patients with reduced precursors, neutrophil response may be diminished (such as those treated with extensive radiotherapy or chemotherapy, or those with bone marrow infiltration by tumour).

- **Graft rejections:**

There have been reports of Graft versus Host Disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation.

Known cases of Hereditary Fructose Intolerance (HFI):

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

Patients with rare hereditary fructose intolerance not be given FILGRASTIM TEVA unless strictly necessary.

Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given FILGRASTIM TEVA.

4.5 Interaction with other medicines and other forms of interaction

The safety and efficacy of FILGRASTIM TEVA given on the same day as myelosuppressive cytotoxic chemotherapy has not been established. In view of the sensitivity of rapidly dividing myeloid cells to myelosuppressive cytotoxic chemotherapy, the use of FILGRASTIM TEVA is not recommended in the period from 24 hours before to 24 hours after chemotherapy.

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

Since lithium promotes the release of neutrophils, it may potentiate the effect of FILGRASTIM TEVA. Although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.

4.6 Fertility, pregnancy and lactation

Pregnancy

FILGRASTIM TEVA is contraindicated in pregnancy and lactation.

The safety of FILGRASTIM TEVA has not been established in pregnant women. Studies in animals have shown reproductive toxicity.

Breastfeeding

The safety of FILGRASTIM TEVA has not been established in lactating women. It is unknown whether the active ingredient, filgrastim, is excreted in human breast milk. Women on FILGRASTIM TEVA should not breastfeed their babies.

4.7 Effects on ability to drive and use machines

FILGRASTIM TEVA can cause fatigue which may affect the ability to drive and use machines. Patients experiencing fatigue may not drive or operate machinery. Patients should be advised not to drive or operate machinery until they know how the FILGRASTIM TEVA affects them.

4.8 Undesirable effects

The most frequent undesirable effects attributable to filgrastim at the recommended dose were mild or moderate musculoskeletal pain, occurring in 10 %, and severe musculoskeletal pain in 3 % of patients. Musculoskeletal pain is usually controlled with standard analgesics. Less frequent undesirable effects include urinary abnormalities predominantly mild or moderate dysuria.

In randomised, placebo-controlled clinical trials, filgrastim did not increase the incidence of undesirable effects associated with cytotoxic chemotherapy. In those clinical trials, undesirable effects reported with equal frequency in patients treated with filgrastim/chemotherapy and placebo/chemotherapy included nausea and

vomiting, alopecia, diarrhoea, fatigue, anorexia (decreased appetite), mucosal inflammation, headache, cough, rash, chest pain, asthenia, pharyngolaryngeal pain (oropharyngeal pain) and constipation.

Blood and lymphatic system disorders:

Less frequent: Splenomegaly, splenic rupture, sickle cell crisis.

Immune system disorders:

Frequent: Hypersensitivity.

Less frequent: Graft versus Host Disease.

Metabolism and nutrition disorders:

Frequent: Blood uric acid increased, blood lactate dehydrogenase increased, anorexia.

Less frequent: Pseudogout.

Nervous system disorders:

Frequent: Headache.

Vascular disorders:

Frequent: Hypotension.

Less frequent: Veno-occlusive disease, fluid volume disturbances, capillary leak syndrome.

Respiratory, thoracic and mediastinal disorders:

Frequent: Oropharyngeal pain, cough, dyspnoea, haemoptysis.

Less frequent: Acute respiratory distress syndrome, respiratory failure, pulmonary oedema, interstitial lung disease, lung infiltration, pulmonary haemorrhage.

Gastrointestinal disorders:

Frequent: Diarrhoea, vomiting, constipation, nausea, mucositis.

Hepatobiliary disorders:

Frequent: Gamma-glutamyl transferase increased, blood alkaline phosphatase increased.

Skin and subcutaneous tissue disorders:

Frequent: Alopecia, skin rash.

Less frequent: Sweets syndrome, cutaneous vasculitis.

Musculoskeletal and connective tissue disorders:

Frequent: Musculoskeletal pain, chest pain.

Less frequent: Exacerbation of rheumatoid arthritis.

Renal and urinary disorders:

Frequent: Dysuria.

Less frequent: Urine abnormality, glomerulonephritis.

General disorders and administration site conditions:

Frequent: Asthenia, fatigue, mucosal inflammation, pain.

Less frequent: unspecified pain, allergic reaction.

Post-marketing:

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.

In the post-marketing setting cutaneous vasculitis has been reported in patients treated with filgrastim. The mechanism of vasculitis in patients receiving filgrastim is unknown.

Less frequent cases of Sweets syndrome (acute febrile dermatosis) have been reported in the post-marketing setting. However, since a significant percentage of these patients were suffering from leukaemia, a condition known to be associated with Sweets syndrome, a causal relationship with FILGRASTIM TEVA has not been established.

In the post-marketing setting, less frequent cases of sickle cell crisis have been reported in patients with sickle cell trait or sickle cell disease (see section 4.4).

Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported in clinical studies and in post marketing experience and were more frequent after IV administration. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship with filgrastim. FILGRASTIM TEVA should be permanently discontinued in patients who experience a serious allergic reaction.

In clinical studies and the post-marketing setting pulmonary adverse effects including interstitial lung disease, pulmonary oedema, and lung infiltration have been reported in some cases with an outcome of respiratory failure or acute respiratory distress syndrome (ARDS), which may be fatal (see section 4.4).

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. Healthcare 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

The effects of FILGRASTIM TEVA overdosage have not been established. Discontinuation of FILGRASTIM TEVA therapy usually results in a 50 % decrease in circulating neutrophils within 1 to 2 days, with a return to normal levels in 1 to 7 days. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL ACTION

5.1 Pharmacodynamic properties

A32.16 Others

Human granulocyte-colony stimulating factor (G-CSF) is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Filgrastim (recombinant methionyl human granulocyte-colony stimulating factor) is produced in *Escherichia coli* K802 by recombinant DNA technology. Filgrastim (r-metHuG-CSF) causes marked increases in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes.

Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50 % within 1 to 2 days, and to normal levels within 1 to 7 days.

5.2 Pharmacokinetic properties

Absorption

After subcutaneous (SC) administration, filgrastim well absorbed, and peak serum concentrations are attained 2 to 8 hours after dosing.

Elimination half-life after IV and SC dosing is usually between 2 and 4 hours. Clearance and half-life are dependent on dose and neutrophil count. When neutrophil-mediated clearance is saturated by high filgrastim concentrations or is diminished by neutropenia, the linear clearance pathway predominates and the pharmacokinetics appear linear. The absolute bioavailability of filgrastim after SC administration is estimated to be 62 % for a 375 µg dose and 75 % for a 750 µg dose. After discontinuation of dosing, filgrastim concentrations decrease to endogenous concentration within 24 hours. A decrease in filgrastim serum concentrations is evidenced upon multiple dosing in healthy subjects and in cancer subjects before chemotherapy. This increase in clearance of filgrastim is dose dependant, and the magnitude of increase appears closely related to the degree of neutrophilia in the recipients, which is consistent with increased neutrophil-mediated clearance by the expanded neutrophil pool. In subjects receiving filgrastim after chemotherapy, plateau serum concentrations are maintained until onset of haemopoietic recovery.

Distribution

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously. Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/mL for 8 to 16 hours. The volume of distribution in blood is approximately 150 mL/kg.

Elimination

Clearance of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous administration. The serum elimination half-life of filgrastim is approximately 3,5 hours, with a clearance rate of approximately 0,6 mL/min/kg.

Specific patient groups

Geriatrics:

Pharmacokinetic data in geriatric patients (> 65 years) are not available.

Renal Impairment:

Studies of filgrastim in patients with moderate impairment of renal function demonstrate that it exhibits a similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances. Higher systemic exposure to filgrastim is observed in patients with end-stage renal disease (ESRD) compared with healthy subjects and subjects with creatinine clearance of 30 to 60 mL/min.

Paediatric population

The pharmacokinetics of filgrastim in paediatric patients after chemotherapy is similar to those in adults receiving the same weight normalised doses, suggesting no age related differences in the pharmacokinetics of filgrastim.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid glacial

Polysorbate 80

Sorbitol

Water for injections

6.2 Incompatibilities

FILGRASTIM TEVA should not be diluted with sodium chloride solution.

This medicine must not be mixed with other products except those mentioned in section 6.6 below.

Diluted FILGRASTIM TEVA may be adsorbed to glass and plastic materials.

6.3 Shelf life

30 months

After dilution: Chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 24 hours between 2 °C and 8 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours between 2 °C and 8 °C.

6.4 Special precautions for storage

Store between 2 °C and 8 °C, in a refrigerator.

Within its shelf-life and for ambulatory use, the product may be removed from the refrigerator (2 °C – 8 °C) and stored at a temperature up to 25 °C for one single period of up to 4 days. If not used within 4 days, the product may be returned to the refrigerator (2 °C – 8 °C) up to the expiry date. Dispose of syringes if stored above 8 °C for more than 4 days.

Do not use FILGRASTIM TEVA after the expiry date which is stated on the outer carton and on the pre-filled syringe.

FILGRASTIM TEVA syringes are for single use only.

For storage conditions after dilution of the medicine, see section 6.3.

Accidental exposure to freezing temperatures does not adversely affect the stability of FILGRASTIM TEVA.

6.5 Nature and contents of container

FILGRASTIM TEVA 30 is available in Type I clear colourless glass pre-filled syringes with a green polypropylene plunger rod and grey bromobutyl rubber plunger stopper, with a permanently attached stainless steel needle with or without a colourless safety device to prevent needle stick injury and re-use.

Available in cardboard carton packs containing 1, 5 or 10 pre-filled syringes with 0,5 mL solution; or Multipacks containing 10 (2 packs of 5) pre-filled syringes with 0,5 mL solution.

FILGRASTIM TEVA 48 is available in Type I clear colourless glass pre-filled syringes with a blue polypropylene plunger rod and grey bromobutyl rubber plunger stopper, with a permanently attached stainless steel needle with or without a colourless safety device to prevent needle stick injury and re-use.

Available in cardboard carton packs containing 1, 5 or 10 pre-filled syringes with 0,8 mL solution; or Multipacks containing 10 (2 packs of 5) pre-filled syringes with 0,8 mL solution.

The syringes with safety device are packed inside cartons either as paper-backed thermoformed PVC blisters or in plastic trays divided into wells, with one syringe per blister or well.

Syringes without safety device are packed in cardboard boxes with cardboard trays.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for dilution:

If required, FILGRASTIM TEVA may be diluted in glucose 50 mg/mL (5 %) solution for infusion.

Dilution to a final concentration less than 0,2 MIU (2 µg) per mL is not recommended at any time.

The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

For patients treated with FILGRASTIM TEVA diluted to concentrations below 1,5 MIU (15 µg) per mL, human serum albumin (HSA) should be added to a final concentration of 2 mg/mL.

Example: In a final injection volume of 20 mL, total doses of FILGRASTIM TEVA less than 30 MIU (300 µg) should be given with 0,2 mL of 200 mg/mL (20 %) human albumin solution added.

When diluted in glucose 50 mg/mL (5 %) solution for infusion, FILGRASTIM TEVA is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

When diluting FILGRASTIM TEVA with 50 mg/ml (5 %) glucose solution or human albumin solution, gently inverse a few times for mixing.

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park

Magwa Crescent West

Waterfall City, Midrand

Gauteng, South Africa

2090

8. REGISTRATION NUMBER(S)

FILGRASTIM TEVA 30: 46/32.16/0317

FILGRASTIM TEVA 48: 46/32.16/0318

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 November 2017

10. DATE OF REVISION OF THE TEXT

To be allocated.