PRODUCT INFORMATION
TEVAGRASTIM

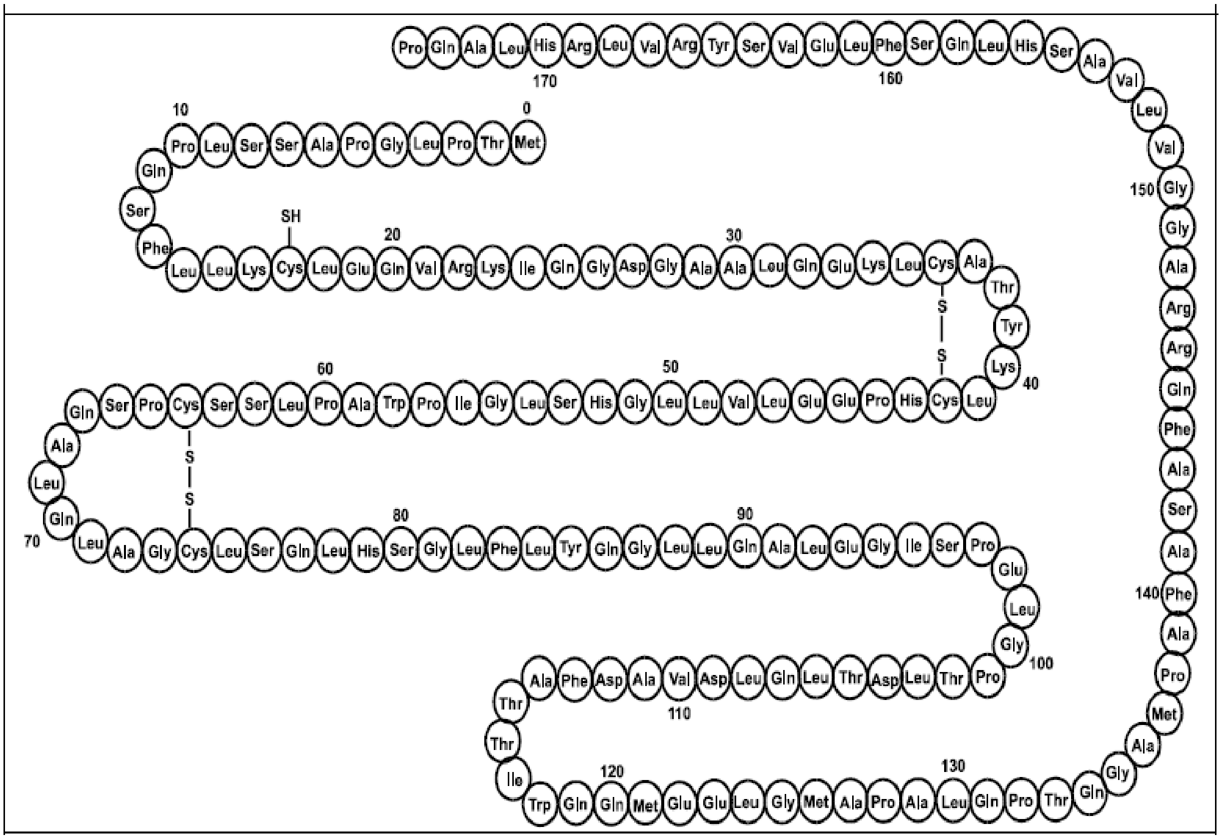
NAME OF THE MEDICINE

Filgrastim (recombinant methionyl human granulocyte colony stimulating factor)

Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. It is produced by *Escherichia coli* bacteria into which has been inserted the human granulocyte colony stimulating factor gene. Filgrastim is unglycosylated and contains an N-terminal methionine necessary for expression in *E. coli*.

Molecular weight: 18,800
CAS no. 121181-53-1

Chemical structure:



DESCRIPTION

TEVAGRASTIM Injections contain 600mcg/mL of filgrastim as the active ingredient. Excipients include glacial acetic acid, polysorbate 80, sodium hydroxide, sorbitol and water for injections.

PHARMACOLOGY

Actions: Colony stimulating factor.

Colony stimulating factors are glycoproteins which act on haemopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation.

Endogenous filgrastim (ie. granulocyte-colony stimulating factor) is a lineage specific colony stimulating factor with selectivity for the neutrophil lineage. Filgrastim is not species specific and has been shown to primarily affect neutrophil progenitor proliferation, differentiation and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing and the increased expression of some functions associated with cell surface antigens).

The pH of filgrastim is 4.12.

Preclinical studies - The results of all preclinical studies indicate that the pharmacological effects of filgrastim are consistent with its predominant role as a regulator of neutrophil production and function.

Comparison of Tevagrastim with Neupogen
Comparability assessment of primary pharmacodynamic *in vitro* studies on receptor binding and biological activity between Tevagrastim and Neupogen, as well as *in vivo* studies in neutropenic mice, healthy rats and monkeys support similar/equivalent pharmacological activity of Tevagrastim compared to Neupogen.

Studies *in vitro*
A comparability study on the binding affinity of Tevagrastim and Neupogen to the human G-CSF receptor using BIAcore analysis demonstrated that the binding of human G-CSF receptor and Tevagrastim or Neupogen was specific and dose dependent, and the results confirmed that the binding affinities of Tevagrastim and Neupogen to the receptor were similar.

A comparison of the biological activity of Tevagrastim relative to that of Neupogen was performed in the murine M-NFS-60 leukaemia cell line. The data indicated that both, Tevagrastim and Neupogen bind to the murine cellular G-CSF receptors with the same affinity and that both preparations are equally effective in inducing a cellular proliferation.

Secondary pharmacodynamic study *in vitro* for determination of proliferation promoting effects of Tevagrastim in comparison to Neupogen on five human malignant cell lines demonstrated that no effect on cell proliferation by both products was found.

Studies *in vivo*
In an *in vivo* cyclophosphamide-induced neutropenic mouse model, the ability of Tevagrastim relative to that of Neupogen in increasing the absolute neutrophil count (ANC) was investigated on days 3 and 5 in two studies. The results of meta-analysis showed that Tevagrastim and Neupogen induced neutrophilia to a similar extent and there was a tendency towards comparable

potencies in terms of the *in vivo* biological activity. *In vivo* studies in neutropenic and non-neutropenic animals, Tevagrastim and Neupogen showed similar primary pharmacological response i.e. increase in ANC.

The pharmacodynamic effects of Tevagrastim and Neupogen in ANC levels were investigated in two phase I studies in healthy volunteers after single dose administration of 5 µg/kg or 10 µg/kg. The first study included only subcutaneous (SC) administration, the second both SC and IV (intravenous) infusion. In both studies, equivalence between Tevagrastim and Neupogen was demonstrated for both the doses after IV or SC administration (Table 1).

Table 1

Treatment Group	**Mean ANC AUC_{0-t} [h*10^9/L]**		**90% CI**	**Point estimate [%]**
	Tevagrastim	**Neupogen**		
Phase I study (1st)				
5 µg/kg SC (n=24)	901.68	901.57	97.8-102.5	100.1
10 µg/kg SC (n=26)	1199.66	1187.85	97.2-104.9	101.0
Phase I study (2nd)				
5 µg/kg SC (n=33)	956.93	983.14	88.23-107.92	97.58
10 µg/kg SC (n=30)	1305.93	1245.18	91.22-120.58	104.88
5 µg/kg IV (n=31)	738.37	776.67	87.47-108.13	97.25
10 µg/kg IV (n=30)	916.96	958.90	80.07-116.45	96.56
Abbreviations: SC = subcutaneous; IV = intravenous				

In the second phase I study there was demonstrated equivalence of Tevagrastim and Neupogen with regard to the pharmacodynamic variable CD34+ count in both the 5 and 10 µg/kg dose groups after single SC injection and IV infusion (Table 2).

Table 2

Treatment Group	**Mean CD34+ AUC_{0-t} [h*/µL]**		**90% CI**	**Point estimate [%]**
	Tevagrastim	**Neupogen**		
Phase I study (2nd)				
5 µg/kg SC (n=33)	1462.63	1448.61	93.29-109.26	100.96
5 µg/kg IV (n=31)	1451.35	1545.21	87.02-101.05	93.77
10 µg/kg SC (n=30)	1860.82	2063.90	84.79-95.87	90.16
10 µg/kg IV (n=30)	1644.85	1525.62	101.37-114.44	107.71
Abbreviations: SC = subcutaneous; IV = intravenous				

Pharmacokinetics

In normal volunteers, serum filgrastim concentrations declined monoexponentially following a single intravenous infusion, exhibiting a half-life of approximately three hours. Clearance and volume of distribution averaged 0.6 mL/minute/kg and 163 mL/kg. Following a single subcutaneous injection, peak serum concentrations of filgrastim occurred at approximately four to six hours. The absorption phase can be fitted to either a zero order or a first order model whereas the elimination phase observed a monoexponential decline. No difference in half-lives was observed following intravenous and subcutaneous doses. The bioavailability was estimated to be approximately 50% following subcutaneous administration.

In cancer patients, clearance and volume of distribution of filgrastim were found to be lower than in normal volunteers, averaging approximately 0.12 to 0.34 mL/minute/kg and 56 to 127 mL/kg, respectively. However, the elimination half-life appeared to be similar when compared to normal volunteers, averaging three to four hours. Following single subcutaneous injections of 3.45 microgram/kg and 11.5 microgram/kg, peak serum concentrations occurred at approximately four to five hours and averaged 4 nanogram/mL and 49 nanogram/mL, respectively. Continuous subcutaneous infusion of filgrastim 23 microgram/kg over 24 hours in cancer patients resulted in a steady-state concentration of approximately 50 (30 to 70) nanogram/mL. No evidence of drug accumulation was observed over 11 to 20 days of continuous infusion. When single intravenous doses (1.73 to 69 microgram/kg) were administered to cancer patients, the area under the serum concentration-time curves (AUC) increased proportional to the dose. Serum concentrations of filgrastim were found to decrease in paediatric cancer patients who were dosed at 5 to 15 microgram/kg/day for ten days. The decrease of serum concentrations may be associated with a change in the clearance of filgrastim due to increasing neutrophil counts.

Subcutaneous injections of filgrastim solutions containing either sorbitol or mannitol resulted in similar pharmacokinetic profiles and response in absolute neutrophil counts (ANC). When single 5 microgram/kg subcutaneous doses were administered to normal subjects using three concentrations of filgrastim solution (300, 600 and 960 microgram/mL), the three concentrations were found to be equivalent in elevating ANC. Although increased maximum serum concentration and AUC were observed with increasing filgrastim concentrations, these pharmacokinetic differences did not correlate with biological response.

Comparison of Tevagrastim with Neupogen
Bioequivalence of Tevagrastim and Neupogen was demonstrated in healthy volunteers at doses of 5 µg/kg and 10 µg/kg bodyweight via either SC injection or IV infusion.
Mean AUC_{0-t} and C_{max} values were similar between treatment groups following SC and IV administration of Tevagrastim and Neupogen in both phase I studies (Table 3 and 4).

Table 3

Treatment Group	**AUC_{0-t} [h*ng/mL]**		**90% CI**	**Point estimate [%]**
	Tevagrastim	**Neupogen**		
Phase I study (1st)				
5 µg/kg SC (n=24)	158.45	143.10	102.7-119.0	110.5
10 µg/kg SC (n=26)	473.91	475.20	93.9-105.9	99.7
Phase I study (2nd)				
5 µg/kg SC (n=33)	157.585	159.426	92.05-105.66	98.63
10 µg/kg SC (n=30)	1056.472	990.996	104.02-115.03	109.39
5 µg/kg IV (n=31)	480.201	470.373	96.55-107.01	101.65
10 µg/kg IV (n=30)	471.148	430.717	102.14-111.30	106.62
Abbreviations: SC = subcutaneous; IV = intravenous				

Table 4

Treatment Group	C_{max} [ng/mL]		90% CI	Point estimate [%]
	Tevagrastim	Neupogen		
Phase I study (1st)				
5 µg/kg SC (n=24)	23.54	21.23	102.2-120.1	110.8
10 µg/kg SC. (n=26)	55.74	56.28	92.1-106.5	99.0
Phase I study (2nd)				
5 µg/kg SC (n=33)	17.976	18.416	87.22-109.10	97.55
5 µg/kg IV (n=31)	129.786	126.124	97.44-107.55	102.37
10 µg/kg SC (n=30)	231.142	221.562	99.30-115.66	107.17
10 µg/kg IV (n=30)	46.239	43.145	100.88-108.41	104.58
Abbreviations: SC = subcutaneous; IV = intravenous				

CLINICAL TRIALS

Cancer patients receiving myelosuppressive chemotherapy

In all clinical studies, administration of filgrastim resulted in a dose dependent rise in neutrophil counts. Following termination of filgrastim therapy, circulating neutrophil counts declined by 50% within one to two days, and to pretreatment levels within one to seven days. Isolated neutrophils displayed normal phagocytic and chemotactic activity in vitro.

In a study of the effects of filgrastim in patients with carcinoma of the urothelium, repeated daily intravenous dosing with filgrastim resulted in a linear dose dependent increase in circulating neutrophil counts over the dose range of 1 to 70 microgram/kg/day. The effects of filgrastim therapy reversed within 24 hours of the termination of administration, and neutrophil counts returned to baseline, in most cases within four days.

In a phase I study of patients with a variety of malignancies, including lymphoma, multiple myeloma and adenocarcinoma of the lung, breast and colon, filgrastim induced a dose dependent increase in neutrophil counts. This increase in neutrophil counts was observed whether filgrastim was administered intravenously (1 to 70 microgram/kg twice daily), subcutaneously (1 to 3 microgram/kg once daily) or by continuous subcutaneous infusion (3 to 11 microgram/kg/day).

These results were consistent with a phase I study of patients with small cell lung cancer who were administered filgrastim prior to chemotherapy. All patients responded to filgrastim (1 to 45 microgram/kg/day), given for five days, with a dose dependent increase in median neutrophil count from a baseline of 9.5 x 10^9/L to a maximum response of 43 x 10^9/L.

In a randomised, double blind, placebo controlled phase III study of small cell lung cancer patients receiving combination chemotherapy (cyclophosphamide, doxorubicin and etoposide), treatment with filgrastim resulted in clinically and statistically significant reductions in both the incidence and duration of infection, as manifested by febrile neutropenia. The incidence, severity and duration of severe neutropenia (absolute neutrophil count (ANC) < 0.5 x 10^9/L) following chemotherapy were all significantly reduced, as were the requirements for inpatient hospitalisation and antibiotic use (see Adverse Reactions). With other myelosuppressive

regimens (e.g. M-VAC, melphalan), a dose dependent increase in neutrophil counts was observed, as well as a decrease in the duration of severe neutropenia.

In a randomised, double blind placebo controlled phase III study of patients with acute myeloid leukaemia (AML), the median duration of neutropenia (ANC < 0.5 x 10^9/L) during the first induction cycle was significantly reduced, from 19 days in the placebo group to 14 days in the filgrastim group. The duration of hospitalisation during induction therapy was also significantly reduced in the filgrastim group, from 29 days to 23 days, as were the duration of fever and incidence of intravenous antibiotic use. Filgrastim had a similar impact on the durations of neutropenia, hospitalisation, fever and intravenous antibiotic use in subsequent cycles of chemotherapy.

The absolute monocyte count was reported to increase in a dose dependent manner in most patients receiving filgrastim. The percentage of monocytes in the differential count was within the normal range. In all studies to date, absolute counts of both eosinophils and basophils were within the normal range following administration of filgrastim. Small non-dose dependent increases in lymphocyte counts following filgrastim administration have been reported in normal subjects and cancer patients.

Peripheral blood progenitor cell (PBPC) collection and therapy
Use of filgrastim, either alone or after chemotherapy, mobilises haemopoietic progenitor cells into the peripheral blood. These PBPCs may be harvested and infused after high dose chemotherapy, either in place of, or in addition to, bone marrow transplantation. Infusion of PBPCs accelerates the rate of neutrophil and platelet recovery, reducing the risk of haemorrhagic complications and the need for platelet transfusions.

In a randomised phase III study of patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing myeloablative chemotherapy, 27 patients received autologous filgrastim mobilised peripheral blood progenitor cell transplantation (PBPCT) followed by filgrastim 5 microgram/kg/day and 31 patients received autologous bone marrow transplantation (ABMT) followed by filgrastim 5 microgram/kg/day. Patients randomised to the filgrastim mobilised PBPCT group, compared to the ABMT group, had significantly fewer median days of platelet transfusions (six versus ten days), a significantly shorter median time to a sustained platelet count > 20 x 10^9/L (16 versus 23 days), a significantly shorter median time to recovery of a sustained ANC greater than or equal to 0.5 x 10^9/L (11 versus 14 days) and a significantly shorter duration of hospitalisation (17 versus 23 days).

In all clinical trials of filgrastim for the mobilisation of PBPCs, filgrastim 5 to 24 microgram/kg/day was administered following infusion of the cells until a sustainable ANC (greater than or equal to 0.5 x 10^9/L) was reached.

Overall, infusion of filgrastim mobilised PBPCs, supported by filgrastim post-transplantation, provided rapid and sustained haematological recovery. Long-term (approximately 100 days) follow-up haematology data from patients treated with autologous PBPCT alone or in combination with bone marrow were compared to historical data from patients treated with ABMT alone. This retrospective analysis indicated that engraftment is durable.
In a randomised trial comparing filgrastim mobilised allogeneic PBPCT with allogeneic BMT in patients with acute leukaemia, chronic myelogenous leukaemia or myelodysplastic syndrome,

filgrastim was given at 10 microgram/kg/day to 163 healthy volunteers for four to five days followed by leukapheresis beginning on day 5. Another 166 healthy volunteers donated bone marrow. The number of CD34+ cells in the leukapheresis product was generally sufficient to support a transplant, with over 80% of donors achieving the target yield of 4 x 106/kg recipient bodyweight. In the vast majority of donors (95%) sufficient PBPCs (2 x 10^6 CD34+ cells/kg of recipient) were obtained in less than or equal to 2 leukaphereses. The median number of CD34+ cells in the leukapheresis product (5.8 x 10^6/kg) was higher than that of bone marrow product (2.7 x 10^6/kg); however, the product from both procedures was sufficient to allow each recipient to receive a transplant. Following transplant, all recipients received filgrastim at 5 microgram/kg/day until neutrophil recovery (up to 28 days). Recipients of allogeneic PBPC had a shorter median time to platelet recovery of greater than or equal to 20 x 10^9/L (15 versus 20 days) and shorter median time to ANC recovery of greater than or equal to 0.5 x 10^9/L (12 versus 15 days). There was no difference in leukaemia free survival at a median follow-up of 12 months.

Patients with severe chronic neutropenia (SCN)
In a randomised, controlled, open label phase III trial of 123 patients with idiopathic, cyclic and congenital neutropenia, untreated patients had a median absolute neutrophil count (ANC) of 0.21 x 10^9/L. Filgrastim therapy was adjusted to maintain the median ANC between 1.5 x 10^9/L and 10 x 10^9/L. A complete response (defined as a median ANC greater than or equal to 1.5 x 10^9/L) was seen in 88% of patients over five months of filgrastim therapy. Overall, the response to filgrastim therapy for all patients was observed in one to two weeks. The median ANC after five months of filgrastim therapy for all patients was 7.46 x 10^9/L (range 0.03 to 30.88 x 10^9/L). In general, patients with congenital neutropenia responded to filgrastim therapy with lower median ANC than patients with idiopathic or cyclic neutropenia.

Overall, daily treatment with filgrastim resulted in clinically and statistically significant reductions in the incidence and duration of fever, infections and oropharyngeal ulcers. As a result, there were also substantial decreases in requirements for antibiotic use and hospitalisation. Additionally, patients treated with filgrastim reported fewer episodes of diarrhoea, nausea, fatigue and sore throat.

Patients with HIV infection
In an open label noncomparative study involving 200 HIV positive patients with neutropenia (ANC < 1.0 x 10^9/L), filgrastim reversed the neutropenia in 98% of patients (ANC greater than or equal to 2 x 10^9/L) with a median time to reversal of two days (range 1 to 16) and a median dose of 1 microgram/kg/day (range 0.5 to 10). 96% of patients achieved reversal of neutropenia with a dose of less than or equal to 300 microgram/day. Normal ANCs were then maintained with a median dose frequency of three 300 microgram vials/week (range 1 to 7). Ganciclovir, zidovudine, co-trimoxazole and pyrimethamine were the medications most frequently considered to be causing neutropenia and 83% of patients received one or more of these on-study. During the study, 84% of these patients were able to increase or maintain dosing of these four medications or add them to their therapy. The number of these four medications received per patient increased by more than 20% (from 0.98 to 1.18) during filgrastim therapy. The median duration of filgrastim treatment was 191 days (range 2 to 815). 153 patients received long-term maintenance therapy (greater than 58 days) and the frequency of dosing was similar to that in the first 30 days of maintenance therapy (71% of patients were receiving two to three vials/week).

Overall, in patients with HIV infection filgrastim rapidly reverses neutropenia and is subsequently able to maintain normal neutrophil counts during chronic administration.

Comparison of Tevagrastim with Neupogen
Biosimilarity between Tevagrastim and Neupogen was demonstrated through the clinical program composed of 5 clinical studies showing the clinical equivalence of both medicinal products. The clinical pharmacology was observed in two phase I studies; clinical efficacy and safety in a pivotal phase III study in patients with breast cancer. Lung cancer and NHL studies in patients focused on safety.

Breast Cancer Study
This was a multinational, multicentre, randomised, controlled phase III study with a total of 348 patients with breast cancer treated with cytotoxic chemotherapy. The study aimed to demonstrate therapeutic equivalence of Tevagrastim and Neupogen.

The primary objective of the study was to compare the effect of Tevagrastim, Neupogen and placebo on the duration of severe neutropenia (DSN) in cycle 1. Secondary endpoints included the incidence of observed neutropenia, the incidence of protocol-defined neutropenia, DSN in cycles 2-4, depth of ANC nadir in cycles 1 to 4, time to ANC recovery in cycles 1 to 4, and safety.

Chemotherapy consisted of a maximum of four cycles of docetaxel 75 mg/m^2 on day 1 and doxorubicin 60 mg/m^2 IV on day 1, repeated every 3 weeks.

The patients were randomised in a ratio 2:2:1 to Tevagrastim, Neupogen, or placebo. The study drugs were injected daily SC from the day after chemotherapy for 5 to a maximum of 14 days or until the ANC reached ≥10 x 10^9/L post-nadir. Placebo patients were switched to filgrastim after completion of first cycle. Blood samples for the determination of ANC were collected within 24 hours prior to chemotherapy and then daily from day 2 to 15 or longer until ANC reached ≥2 x 10^9/L. In cycle 1 mean of DSN was statistically significantly longer for the placebo group than for the Tevagrastim and Neupogen groups and confirmed the significantly superior activity of Tevagrastim compared with placebo and equivalence to Neupogen.

The incidence of febrile neutropenia (FN) in cycle 1 was considerably lower in Tevagrastim and Neupogen groups compared with placebo (12.1 % vs. 12.5 % vs. 36.1 %). There were no relevant differences between Tevagrastim and Neupogen in the incidence of FN in cycle 1 or across all cycles.

ANC over time in cycle 1 in Tevagrastim and Neupogen study groups increased abruptly after day 2 to achieve a maximum on day 3, then fell to a mean ANC nadir 0.7 x 10^9/L on day 7 and reached a second maximum on day 11. In placebo group, there was no initial increase, but ANC decreased steadily from day 2 and fell to a considerably deeper mean nadir of 0.2 x 10^9/L on day 11. In cycle 1, the median time to ANC recovery was similar in the Tevagrastim and Neupogen groups (8.0 days) and shorter in the placebo group (15.0 days). In cycles 2 to 4, the mean ANC nadir was not as deep as in the first cycle and similar for all study groups (1.0 x 10^9/L). Median time to ANC recovery was also similar (8.0 days). Full analysis set for the study is presented in Table 7.

In this phase III trial Tevagrastim was shown to be superior to placebo and as effective as Neupogen in reducing the duration of chemotherapy-induced severe neutropenia, the depth of the ANC nadir, and time to ANC recovery. Both medicinal products were equally effective in reducing the incidence of febrile neutropenia, had low immunogenicity and were well tolerated with no un-expected drug-related adverse events.

Lung cancer study
Multinational, multicentre, randomized Phase III clinical trial was conducted in 240 patients with lung cancer treated with cytotoxic chemotherapy.

The primary objective of the trial was to assess safety in cycle 1 in comparison with Neupogen. Efficacy endpoints included the DSN, the incidence of FN, and the depth of ANC nadir (ANC_{min}) in cycles 1 and 4; and time to ANC recovery (t_{rec}) in cycles 1 and 4.

The patients received a maximum of 6 cycles of chemotherapy every 3 or 4 weeks, depending on the regimen. Chemotherapy was started on day 1 of each cycle. The most common chemotherapy regimen used was cisplatin plus etoposide or gemcitabine. Other regimens included cisplatin plus vinorelbine and combinations of carboplatin with vinorelbine, etoposide, gemcitabine, or paclitaxel.

The patients were randomised in a 2:1 ratio to primary filgrastim prophylaxis with Tevagrastim or Neupogen during cycle 1, administrating of 5 μg/kg/day. Patients in the reference group were switched to Tevagrastim after completion of cycle 1. The study drugs were injected daily SC for at least 5 days to a maximum of 14 days, starting 24 hours after the last chemotherapy. Filgrastim prophylaxis discontinued when ANC of $\geq 10 \times 10^9$/L was reached.

In this phase III trial primary prophylaxis with Tevagrastim and Neupogen was shown to be equally effective and safe. ANC profiles were very similar. Minor, non significant differences between both drugs were noticed in the time to ANC recovery and the incidence of FN, which explained by differences in patient characteristics. The typical side effects reported occurred with either preparation. The full analysis set for the study is presented in Table 7.

Non-Hodgkin Lymphoma
This was multinational, multicenter, investigator-blinded, randomized phase III trial of Tevagrastim versus Neupogen in patients with aggressive non-Hodgkin lymphomas.

The study aimed to compare Tevagrastim with Neupogen with regard to safety and clinical efficacy in the treatment of chemotherapy induced neutropenia. Efficacy endpoints included DSN, the incidence of observed or protocol-defined FN, depth of ANC nadir in cycles 1 and 4, and time to ANC recovery in cycles 1 and 4. The safety evaluation was assessed based on AEs, laboratory tests, physical examination, and vital signals.

Patients received a maximum of 6 cycles of Cyclophosphamide-Hydroxydaunomycin (Adriamycin)-Oncovin (Vincristine)-Prednisolon (CHOP) chemotherapy every 3 weeks. Additional treatment with the anti-CD20 monoclonal antibody rituximab was at the discretion of the treating physician.

The patients were randomised to treatment with Tevagrastim or Neupogen during cycle 1, administrating 5 μg/kg/day. The study drugs were injected daily SC for at least 5 days to a maximum of 14 days, starting 24 hours after the last chemotherapy. Study drugs were discontinued when ANC of $\geq 10 \times 10^9$/L was reached.

The study data confirmed that primary prophylaxis with Tevagrastim is as effective as the Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia. The ANC profiles were similar over the course of 1 chemotherapy cycle. The safety profiles were comparable. Full analysis set for the study is presented in Table 7.

Table 7: Duration of Severe Neutropenia and Incidence of Febrile Neutropenia Across Studies: Full Analysis Set

Study Name Indication	**Breast Cancer Study**			**Lung Cancer Study**		**Non-Hodgkin Lymphoma Study**	
Treatment Group	**T**	**N**	**P***	**T**	**N**	**T**	**N**
[n]	140	136	72	160	80	63	29
Mean DSN [days]							
Cycle 1	1.1	1.1	3.8	0.5	0.3	0.5	0.9
ANCOVA [CI]#	0.028 [-0.261, 0.316]			0.157 [-0.114, 0.428]		-0.378 [-0.837, 0.081]	
Cycle 4	0.7	0.7	0.6	0.4	0.3	0.2	0.7
Incidence of FN [%]							
Cycle 1	12.1	12.5	36.1	15.0	8.8	11.1	20.7
Across all cycles	20.7	22.1	41.7	33.1	23.8	31.7	41.4

Abbreviations: T = Tevagrastim, N = Neupogen, P = Placebo.
DSN = duration of severe neutropenia; FN = Observed or protocol-defined febrile neutropenia; ANCOVA = analysis of covariance; CI = confidence interval;
* - patients in this groups received Tevagrastim in all cycles after cycle 1
# ANCOVA estimate and 2-sided 95% confidence interval for difference Tevagrastim-Neupogen in cycle 1

INDICATIONS

To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs in doses not usually requiring bone marrow transplantation.

To reduce the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia.

For the mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy, in order to accelerate neutrophil and platelet recovery by

infusion of such cells after myeloablative or myelosuppressive therapy in patients with nonmyeloid malignancies.

For the mobilisation of peripheral blood progenitor cells, in normal volunteers, for use in allogeneic peripheral blood progenitor cell transplantation.

In patients receiving myeloablative chemotherapy, to reduce the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation.
For chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia.

In patients with HIV infection, for reversal of clinically significant neutropenia and subsequent maintenance of adequate neutrophil counts during treatment with antiviral and/or other myelosuppressive medications.

CONTRAINDICATIONS

Known hypersensitivity to *E. coli* derived products, filgrastim, or any other component of the product.

PRECAUTIONS

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

Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced include 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 G-CSF.

Adult respiratory distress syndrome (ARDS)

There have been occasional reports of the occurrence of adult respiratory distress syndrome (ARDS) in patients receiving filgrastim. 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 leading to respiratory failure or ARDS.

Pulmonary Haemorrhage and Haemoptysis

Pulmonary haemorrhage manifesting as pulmonary infiltrates and haemoptysis requiring hospitalization have been reported in patients and donors receiving human G-CSF. Haemoptysis resolved with discontinuation of human G-CSF.

As with other haemopoietic growth factors, granulocyte colony stimulating factor (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 nonmyeloid cells in vitro.

Splenic rupture has been reported in both healthy donors and patients with cancer following administration of filgrastim; some of these cases were fatal. Left upper abdominal pain and/or shoulder tip pain accompanied by rapid increase in spleen size should be carefully monitored due to the rare but serious risk of splenic rupture.

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.

Special warnings
TEVAGRASTIM should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens (see below).

TEVAGRASTIM should not be administered to patients with severe congenital neutropenia (Kostman's syndrome) with abnormal cytogenetics (see below).

Sickle cell disease
Clinicians should exercise caution and monitor patients accordingly when administering filgrastim to patients with sickle cell disease because of the reported association of filgrastim with sickle cell crisis (in some cases fatal). Use of filgrastim in patients with sickle cell disease should be considered only after careful evaluation of the potential risks and benefits.

Severe chronic neutropenia
Cytogenetic abnormalities, transformation to myelodysplasia (MDS) and acute myeloid leukaemia (AML) have been observed in patients treated with filgrastim for severe chronic neutropenia (SCN). Myelodysplasia and AML have been reported to occur in the natural history of SCN without cytokine therapy. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia (see Adverse Reactions). Abnormal cytogenetics have been associated with the development of myeloid leukaemia. The effect of filgrastim on the development of abnormal cytogenetics and the effect of continued filgrastim administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or MDS, the risks and benefits of continuing filgrastim should be carefully considered.

Thrombocytopenia
Thrombocytopenia has been reported commonly ($\geq 1/100$ and $< 1/10$) in patients receiving filgrastim. Regular monitoring of the platelet count is recommended.

Myelodysplasia and leukaemia
The safety and efficacy of filgrastim administration in patients with myelodysplasia or chronic myeloid leukaemia receiving myelosuppressive chemotherapy without stem cell support have not been established.

Randomised studies of filgrastim in patients undergoing chemotherapy for acute myeloid leukaemia demonstrate no stimulation of disease as measured by remission rate, relapse and survival.

Cancer patients receiving myelosuppressive chemotherapy

Concurrent use with chemotherapy and radiotherapy

The safety and efficacy of filgrastim given concurrently with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, the use of filgrastim is not recommended in the period 24 hours before to 24 hours after the administration of chemotherapy (see Dosage and Administration).

No controlled study has been done to examine the combination of chemoradiotherapy and filgrastim on platelet count in a suitable oncology setting. Therefore, until more definitive data are available, simultaneous use of filgrastim with chemoradiation should be undertaken with caution.

Leucocytosis

White blood cell counts of 100 x 10^9/L or greater were observed in approximately 2% of patients receiving filgrastim at doses above 5 microgram/kg/day. There were no reports of adverse events associated with this degree of leucocytosis. In order to avoid the potential complications of excessive leucocytosis, a full blood count is recommended twice per week during filgrastim therapy (see Laboratory monitoring).

Premature discontinuation of filgrastim therapy

A transient increase in neutrophil counts is typically seen one to two days after initiation of filgrastim therapy. However, for a sustained therapeutic response, filgrastim therapy should be continued until the post nadir absolute neutrophil count reaches 10 x 10^9/L. Therefore, the premature discontinuation of filgrastim therapy, prior to the time of recovery from the expected neutrophil nadir, is generally not recommended (see Dosage and Administration).

Other

In studies of filgrastim administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see Adverse Reactions). Because of the potential for receiving higher doses of chemotherapy (i.e. full doses on the prescribed schedule for a longer period), the patient may be at greater risk of thrombocytopenia, which should be monitored for carefully. Anaemia and nonhaematological consequences of increased chemotherapy doses (please refer to the prescribing information of the specific chemotherapy agents used) may also occur. Regular monitoring of the haematocrit and platelet count is recommended. Furthermore, care should be exercised in the administration of filgrastim in conjunction with drugs known to lower the platelet count and in the presence of moderate or severe organ impairment. Thrombocytopenia may be more severe than normal in later courses of chemotherapy.

The use of filgrastim mobilised peripheral blood progenitor cells has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

Peripheral blood progenitor cell collection and therapy

Mobilisation

There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between both different patient groups and results of laboratory assays of CD34+ cells means that direct comparison between different studies is difficult and an optimum method cannot yet be recommended. The choice of mobilisation method should be considered in relation to the overall objectives of treatment for an individual patient.

Assessment of progenitor cell yields

In assessing the number of progenitor cells harvested in patients treated with filgrastim, particular attention should be paid to the method of quantitation. The results of flow cytometric analysis of CD34+ cell numbers vary depending on the precise methodology used. Recommendations for minimum acceptable progenitor cell yield based on studies using methods other than that of the reporting laboratory need to be interpreted with caution.

Statistical analysis of the relationship between the number of CD34+ cells infused and the rate of platelet recovery after high dose chemotherapy indicates a complex but continuous relationship, with the probability of more rapid platelet recovery increasing as the CD34+ cell yield increases. Currently, the minimum acceptable yield of CD34+ cells is not well defined. The recommendation of a minimum yield of greater than or equal to 2×10^6 CD34+ cells/kg is based on published experience resulting in adequate haematological reconstitution.

Prior exposure to cytotoxic agents

Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of peripheral blood progenitor cells to achieve the recommended minimum yield (greater than or equal to 2×10^6 CD34+ cells/kg) or acceleration of platelet recovery to the same degree. When peripheral blood progenitor cell transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitor cells mobilised in such patients before the administration of high dose chemotherapy.

In one phase II study in heavily pretreated patients with acute lymphoblastic leukaemia, non-Hodgkin's lymphoma or Hodgkin's disease, no increased yield of progenitor cells was demonstrated by increasing the dose of filgrastim beyond that recommended.

If yields are inadequate, as measured by the criterion above, alternative forms of treatment not requiring progenitor cell support should be considered.

Some cytotoxic agents exhibit particular toxicities to the haemopoietic progenitor pool, and may adversely affect progenitor cell mobilisation. Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor cell mobilisation, may reduce progenitor cell yield. Nevertheless, the administration of melphalan, carboplatin or BCNU together with Neupogen has been shown to be effective for progenitor cell mobilisation.

Leucocytosis

During the period of administration of filgrastim for peripheral blood progenitor cell mobilisation in cancer patients, discontinuation of filgrastim is appropriate if the leucocyte count rises to > 100 x 10^9/L. (See Sickle Cell disease).

Tumour contamination of bone marrow and leukapheresis products

Some studies of patient bone marrow and leukapheresis products have demonstrated the presence of malignant cells. While the possibility exists for tumour cells to be released from the marrow during mobilisation of peripheral blood progenitor cells and subsequently collected in the leukapheresis product, in most of the studies, leukapheresis products appear to be less contaminated than bone marrow from the same patient. The effect of reinfusion of tumour cells has not been well studied, and the limited data available are inconclusive.

Normal donors undergoing peripheral blood progenitor cell mobilisation

Mobilisation of PBPC does not provide a direct clinical benefit to normal donors and should only be considered for the purposes of allogeneic stem cell transplantation.

PBPC mobilisation should be considered only in donors who meet normal clinical and laboratory eligibility criteria for stem cell donation with special attention to haematological values and infectious disease.

The safety and efficacy of filgrastim has not been assessed in normal donors < 16 years or > 60 years.

Transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, two cases of platelets < 50 x 10^9/L were reported and attributed to the leukapheresis procedure.

If more than one leukapheresis is required, particular attention should be paid to donors with platelets < 100 x 10^9/L prior to leukapheresis; in general apheresis should not be performed if platelets are < 75 x 10^9/L.

Leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis.

Filgrastim administration should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 100 x 10^9/L.

Donors who receive filgrastim for PBPC mobilisation should be monitored until haematological indices return to normal.

Insertion of a central venous catheter should be avoided where possible, therefore consideration should be given to the adequacy of venous access when selecting donors.

Long-term safety follow-up of donors is ongoing. For up to four years, there have been no reports of abnormal haemopoiesis in normal donors. Nevertheless, a risk of promotion of a malignant myeloid clone cannot be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors to ensure monitoring of long-term safety.

There have been uncommon (≥ 1/1000 and < 1/100) cases of splenic rupture reported in healthy donors following administration of G-CSFs. In donors experiencing left upper abdominal pain and/or shoulder tip pain and rapid increase in spleen size, the risk of splenic rupture should be considered and carefully monitored.

In normal donors, pulmonary adverse events (haemoptysis, pulmonary infiltrates) have been reported very rarely (< 0.01%).

Recipients of allogeneic peripheral blood progenitor stem cells mobilised with filgrastim
Current data indicate that immunological interactions between the allogeneic PBPC graft and the recipient may be associated with an increased risk of acute and chronic graft versus host disease (GvHD) when compared with bone marrow transplantation.

Severe chronic neutropenia
Diagnosis
Care should be taken to confirm the diagnosis of severe chronic neutropenia (SCN), which may be difficult to distinguish from myelodysplasia, before initiating filgrastim therapy. The safety and efficacy of filgrastim in the treatment of neutropenia or pancytopenia due to other haemopoietic disorders (e.g. myelodysplastic disorders or myeloid leukaemia) have not been established.

It is therefore essential that serial full blood counts, with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype be performed prior to initiation of filgrastim therapy. The use of filgrastim prior to diagnostic confirmation of SCN may mask neutropenia as a diagnostic sign of a disease process other than SCN and prevent adequate evaluation and appropriate treatment of the underlying condition causing the neutropenia.

Patients with HIV infection
Risks associated with increased doses of myelosuppressive medications
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medications. As a result of the potential to receive higher doses or a greater number of medications with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended (see Laboratory monitoring, Patients with HIV infection).

Infections and malignancies causing myelosuppression
Neutropenia may also be due to bone marrow infiltrating opportunistic infections such as Mycobacterium avium complex or malignancies such as lymphoma. In patients with known bone marrow infiltrating infection or malignancy, consideration should be given to appropriate therapy for treatment of the underlying condition. The effects of filgrastim on neutropenia due to bone marrow infiltrating infection or malignancy have not been been well established.

Effect on laboratory tests
Cancer patients receiving myelosuppressive chemotherapy
A full blood count, haematocrit and platelet count should be obtained prior to chemotherapy and at regular intervals (twice per week) during TEVAGRASTIM therapy. Following cytotoxic chemotherapy, the neutrophil nadir occurred earlier during cycles when filgrastim was

administered, and white blood cell differentials demonstrated a left shift, including the appearance of promyelocytes and myeloblasts. In addition, the duration of severe neutropenia was reduced, and was followed by an accelerated recovery in the neutrophil counts. Therefore, regular monitoring of white blood cell counts, particularly at the time of the recovery from the postchemotherapy nadir, is recommended in order to avoid excessive leucocytosis (see Dosage and Administration).

Peripheral blood progenitor cell collection and therapy
After four days of TEVAGRASTIM treatment for peripheral blood progenitor cell mobilisation, neutrophil counts should be monitored. Frequent complete blood counts and platelet counts are recommended following infusion of peripheral blood progenitor cells, at least three times per week until haemopoietic recovery.

The mobilisation and apheresis procedures should be performed in collaboration with an oncology/ haematology centre with acceptable experience in this field and where the monitoring of haemopoietic progenitor cells can be appropriately performed and interpreted (see Precautions, Peripheral blood progenitor cell collection and therapy).

Severe chronic neutropenia
During the initial four weeks of TEVAGRASTIM therapy and for two weeks following any dose adjustment, a full blood count (FBC) with differential count should be performed twice weekly. Once a patient is clinically stable, a full blood count with differential count and platelet determination should be performed monthly during the first year of treatment. Thereafter, if clinically stable, routine monitoring with regular FBCs (i.e. as clinically indicated but at least quarterly) is recommended. Additionally, for those patients with congenital neutropenia, annual bone marrow and cytogenetic evaluations should be performed throughout the duration of treatment (see Warnings, Adverse Reactions).

In clinical trials, the following laboratory results were observed:
Cyclic fluctuations in the neutrophil counts were frequently observed in patients with congenital or idiopathic neutropenia after initiation of filgrastim therapy.

Platelet counts were generally at the upper limits of normal prior to filgrastim therapy. With filgrastim therapy, platelet counts decreased but generally remained within normal limits (see Adverse Reactions).

Early myeloid forms were noted in peripheral blood in most patients, including the appearance of metamyelocytes and myelocytes. Promyelocytes and myeloblasts were noted in some patients. Relative increases were occasionally noted in the number of circulating eosinophils and basophils. No consistent increases were observed with filgrastim therapy.

HIV infection
Absolute neutrophil count should be monitored closely, especially during the first few weeks of TEVAGRASTIM therapy. Some patients may respond very rapidly with a considerable increase in neutrophil count after initial doses of TEVAGRASTIM. It is recommended that the ANC is measured daily for the first two to three days of TEVAGRASTIM administration. Thereafter, it is recommended that the ANC is measured at least twice per week for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During

intermittent dosing with TEVAGRASTIM 300 microgram, there will be wide fluctuations in the patient's ANC over time. In order to determine a patient's trough or nadir ANC, it is recommended that blood samples for ANC measurement are obtained immediately prior to any scheduled dosing with TEVAGRASTIM.

Carcinogenesis, genotoxicity, effects on fertility

The carcinogenic potential of filgrastim has not been studied. In either the presence or absence of a drug enzyme metabolising system, filgrastim failed to induce chromosomal aberrations (in Chinese hamster lung cells in vitro) or bacterial gene mutations. Filgrastim was negative in an in vivo mouse micronuclear test. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolising enzyme system. Filgrastim had no observed effect on the fertility of male or female rats, or gestation at doses up to 500 microgram/kg.

No human data are available.

Use in pregnancy (Category B3)

There are no company sponsored studies of the use of TEVAGRASTIM in pregnant women. However, there are cases in the literature where the transplacental passage of filgrastim has been demonstrated. TEVAGRASTIM should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

Reproductive studies in pregnant rats have shown that filgrastim was not associated with lethal, teratogenic or behavioural effects on fetuses when administered by daily intravenous injection during the period of organogenesis at dose levels up to 575 microgram/kg/day. The administration of filgrastim to pregnant rabbits during the period of organogenesis at doses of 20 microgram/kg/day intravenously, or greater, was associated with an increased incidence of embryonic loss, urogenital bleeding and decreased food consumption. External abnormalities were not observed in the fetuses of treated does, but there was a significant increase in the incidence of fusion of sternebrae at an 80 microgram/kg/day dose. The administration of filgrastim to pregnant rabbits at a dose of 5 microgram/kg/day intravenously was not associated with observable adverse effects to the doe or fetus.

Use in lactation

It is not known whether filgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised in the use of TEVAGRASTIM in breastfeeding women.

Use in children

Long-term follow-up data are available from a postmarketing surveillance study in SCN patients including 32 infants, 200 children and 68 adolescents. The data suggest that height and weight are not adversely affected in paediatric patients who received up to five years of filgrastim treatment. Limited data from patients who were followed in a phase 3 study to assess the safety and efficacy of filgrastim in SCN for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

Paediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocytosis or Schwachman Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic filgrastim

treatment. The relationship of these events to TEVAGRASTIM administration is unknown (see Warnings, Adverse Reactions).

Although use in children with acute myeloid leukaemia is not excluded, published experience is limited and safety has not been clearly established.

Use in elderly
Clinical trials with filgrastim 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.

Patients with renal or hepatic impairment
Studies of filgrastim in patients with severe impairment of renal or hepatic function demonstrate that it exhibits a similiar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances.

INTERACTIONS WITH OTHER MEDICINES

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

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

Cancer patients receiving myelosuppressive chemotherapy
Chronic administration
No evidence of interaction of filgrastim with other drugs was observed in the course of clinical trials (see Precautions, Myelosuppressive chemotherapy, Concurrent use with chemotherapy and radiotherapy).

ADVERSE EFFECTS

Cancer patients receiving myelosuppressive chemotherapy
In clinical trials involving over 200 patients receiving filgrastim following cytotoxic chemotherapy, most adverse experiences were the sequelae of the underlying malignancy or cytotoxic chemotherapy. In all phase II/III trials, medullary bone pain was the only consistently observed adverse reaction attributed to filgrastim therapy, reported in 24% of patients. This bone pain was generally reported to be of mild to moderate severity, and could be controlled in most patients with non-narcotic analgesics; infrequently, bone pain was severe enough to require narcotic analgesics. Bone pain was reported more frequently in patients treated with higher doses (20 to 100 microgram/kg/day) administered intravenously, and less frequently in patients treated with lower subcutaneous doses of filgrastim (3 to 10 microgram/kg/day).

In the randomised, double blind, placebo controlled trial of filgrastim therapy following combination chemotherapy in patients with small cell lung cancer, the adverse events shown in

Table 1 were reported to be possibly, probably or definitely related to the double blind study medication (placebo or filgrastim at 4 to 8 microgram/kg/day).

Table 8 – Clinical adverse events reported to be related to double blind study medication

Body system	Percentage of patients	
	Placebo (n=68)	Filgrastim (n=69)
Musculoskeletal	1.5	12.0
Dermatological	6.0	6.0
Body as a whole	5.0	4.3
Neurological/psychiatric	3.0	4.3
Respiratory	1.5	3.0
Vascular disorders	1.5	3.0
Local reaction	1.5	1.4
Thrombocytopenia/coagulation	2.9	Not reported
Autonomic nervous system	Not reported	1.4
Special senses	Not reported	1.4

In this study, there were no serious, life threatening or fatal adverse reactions attributed to filgrastim therapy. Specifically, there were no reports of flu-like symptoms, pleuritis, pericarditis or other major systemic reactions to filgrastim.

Spontaneously reversible elevations in uric acid, lactate dehydrogenase and alkaline phosphatase occurred in 26 to 56% of patients receiving filgrastim following cytotoxic chemotherapy; these elevations were not reported to be associated with clinical adverse events.

The occurrence of stomatitis and diarrhoea in patients receiving allogeneic transplants is consistent with the use of myeloablative chemotherapy. In a study of 70 patients undergoing allogeneic bone marrow transplantation in which 33 patients were randomised to the placebo group and 37 to the filgrastim group, the incidence and severity of diarrhoea and stomatitis increased from the pretransplant to the post-transplant period in both the placebo and filgrastim treated patients. Prior to transplantation, 12 patients randomised to the placebo group and six patients randomised to filgrastim reported moderate to severe diarrhoea. Following transplantation, the incidence of moderate to severe diarrhoea increased to 23 and 14 patients respectively. No patients in either group experienced moderate or severe stomatitis prior to transplantation, while after transplantation, 19 patients in the placebo group and eight patients in the filgrastim group reported moderate to severe stomatitis.

In a randomised double blind placebo controlled phase III study of patients with acute myeloid leukaemia, there were three patients reported to have developed ARDS during the study (two filgrastim, one placebo). This is a rare but expected event in this patient population, and all three patients had recognised predisposing factors. As a causal relationship between the development of ARDS and filgrastim treatment has not been established, and as multiple risk factors are often present, any decision to discontinue filgrastim in this setting should be based on the overall assessment of contributing factors.

Cases of capillary leak syndrome have been reported uncommonly (≥1/1000 to < 1/100).

Rare cases (>0.01% and <0.1%) of Sweet's syndrome (acute febrile dermatosis) have been reported.

Very rare (estimated 0.03 cases per 100,000 exposures [0.00003%]) events of pseudogout have been reported in patients with cancer treated with filgrastim.

Chronic administration

With chronic administration, clinical splenomegaly has been reported in 30% of patients. Less frequently observed adverse events included exacerbation of some pre-existing skin disorders (e.g. psoriasis), cutaneous vasculitis (leucocytoclastic), alopecia, haematuria/ proteinuria, thrombocytopenia (platelets < 50 x 10^9/L) and osteoporosis. Patients receiving chronic treatment with TEVAGRASTIM should be monitored periodically for the appearance of these conditions.

No evidence of interaction of filgrastim with other drugs was observed in the course of clinical trials (see Precautions, Concurrent use with chemotherapy and radiotherapy). Since commercial introduction of filgrastim, there have been rare reports (< 1 in 100,000 administrations) of symptoms suggestive of allergic type reactions, such as anaphylaxis, dyspnoea, hypotension, skin rash and urticaria, but in which an immune component has not been demonstrated. Approximately half occurred following the initial dose; reactions occurred more frequently with intravenous administration. Symptoms recurred in some patients who were rechallenged. There have been rare reports (< 1 in 500,000 administrations) of cutaneous vasculitis. TEVAGRASTIM should be permanently discontinued in patients who experience a serious allergic reaction.

In chronically treated patients, including some who have received filgrastim daily for almost two years, there has been no evidence of the development of antibodies to filgrastim or a blunted or diminished response over time.

Peripheral blood progenitor cell collection and therapy

Filgrastim mobilised autologous peripheral blood progenitor cell collection

In clinical trials, 126 patients have received filgrastim for mobilisation of peripheral blood progenitor cells. During the mobilisation period, adverse events related to filgrastim consisted primarily of mild to moderate musculoskeletal symptoms, reported in 44% of patients. These symptoms were predominantly events of medullary bone pain (38%). Headache was reported related to filgrastim in 7% of patients. Mild to moderate transient increases in alkaline phosphatase levels were reported related to filgrastim in 21% of the patients who had serum chemistries evaluated during the mobilisation phase.

All patients had increases in neutrophil counts consistent with the biological effects of filgrastim. Two patients had a white blood cell count greater than 100 x 10^9/L with white blood cell count increases during the mobilisation period ranging from 16.7 x 10^9/L to 138 x 10^9/L above baseline. 88% of patients had an increase in white blood cell count between 10 x 10^9/L and 70 x 10^9/L above baseline. No clinical sequelae were associated with any grade of leucocytosis.

65% of patients had downward shifts in haemoglobin, which were generally mild to moderate (59%), and 97% of patients had decreases in platelet counts related to the leukapheresis procedure. Only two patients had platelet counts less than 50 x 10^9/L.

Allogeneic peripheral blood progenitor cell mobilisation in normal donors
The most commonly reported adverse event was mild to moderate transient musculoskeletal pain. Leucocytosis (WBC > 50 x 10^9/L) was observed in 41% of donors and transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim and leukapheresis was observed in 35% of donors.

Transient, minor increases in alkaline phosphatase, LDH, AST and uric acid have been reported in normal donors receiving filgrastim; these were without clinical sequelae.

Exacerbation of arthritic symptoms has been observed very rarely.

Symptoms suggestive of severe allergic reactions have been reported very rarely.

Headaches, believed to be caused by filgrastim, have been reported in PBPC donor studies.

There have been uncommon (≥ 1/1000 and < 1/100) cases of splenic rupture reported in normal donors receiving G-CSFs (see Precautions).

Cases of capillary leak syndrome have been reported uncommonly (≥1/1000 to < 1/100).

In normal donors, pulmonary adverse events (haemoptysis, pulmonary infiltrates) have been reported very rarely (< 0.01%).

Peripheral blood progenitor cell transplantation supported by filgrastim
During the period of filgrastim administration after infusion of autologous peripheral blood progenitor cells, filgrastim was administered to 110 patients as supportive therapy and adverse events were consistent with those expected after high dose chemotherapy. Mild to moderate musculoskeletal pain was the most frequently reported adverse event related to filgrastim, reported in 15% of patients. In patients receiving allogeneic PBPCs, a similar incidence of musculoskeletal pain was reported.

Severe chronic neutropenia
The safety and efficacy of chronic daily administration of filgrastim in patients with severe chronic neutropenia have been established in phase I/II clinical trials of 74 patients treated for up to three years, and in a phase III trial of 123 patients treated for up to two years.

Mild to moderate bone pain was reported in approximately 33% of patients in clinical trials. This symptom was readily controlled with mild analgesics. General musculoskeletal pain was also noted in higher frequency in patients treated with filgrastim.

Palpable splenomegaly was observed in approximately 30% of patients. Abdominal or flank pain was seen infrequently and thrombocytopenia (< 50 x 10^9/L) was noted in 12% of patients with palpable spleens. Less than 3% of all patients underwent splenectomy, and most of these had a prestudy history of splenomegaly. Less than 6% of patients had thrombocytopenia (< 50 x 10^9/L)

during filgrastim therapy, most of whom had a prestudy history. In most cases, thrombocytopenia was managed by filgrastim dose reduction or interruption. There were no associated serious haemorrhagic sequelae in these patients. Epistaxis was noted in 15% of patients treated with filgrastim, but was associated with thrombocytopenia in 2% of patients. Anaemia was reported in approximately 10% of patients, but in most cases appeared to be related to frequent diagnostic phlebotomy, chronic illness or concomitant medications.

Cytogenetic abnormalities, transformation to myelodysplasia and acute myeloid leukaemia have been observed in patients treated with filgrastim for severe chronic neutropenia (SCN) (see Precautions, Severe chronic neutropenia). Based on analysis of data from a postmarketing surveillance study of 531 SCN patients with an average follow-up of 4.0 years, the risk of developing these abnormalities (cytogenetic abnormalities, myelodysplasia and AML) appears to be confined to the subset of patients with congenital neutropenia. A life table analysis of these data revealed that the cumulative risk of developing leukaemia or MDS by the end of the eighth year of Neupogen treatment in a patient with congenital neutropenia was 16.5% which is an annual rate of approximately 2%.

Cytogenetic abnormalities, including monosomy 7, have been reported in patients treated with filgrastim who had previously documented normal cytogenetic evaluations. It is unknown whether the development of cytogenetic abnormalities, myelodysplasia or AML is related to chronic daily filgrastim administration or to the natural history of SCN. It is also unknown if the rate of conversion in patients who have not received filgrastim is different from that of patients who have received filgrastim. Routine monitoring through regular FBCs is recommended for all SCN patients. Additionally, annual bone marrow and cytogenetic evaluations are recommended in all patients with congenital neutropenia (see Precautions, Laboratory monitoring).

Other adverse events infrequently observed and possibly related to filgrastim therapy were injection site reaction, headache, hepatomegaly, arthralgia, osteoporosis, rash, alopecia, cutaneous vasculitis and haematuria/ proteinuria. Patients receiving chronic treatment with filgrastim should be monitored periodically for the appearance of these conditions.

HIV infection

In three clinical studies involving a total of 244 HIV positive patients, the only adverse events that were consistently considered related to filgrastim administration were musculoskeletal pain, predominantly mild to moderate bone pain and myalgia. In the largest of the three studies involving 200 patients, the event rate was 12%. This is consistent with the 14% incidence of musculoskeletal pain reported in clinical trials in other indications where doses of 0.35 to 11.5 microgram/kg/day were used. The incidence of severe musculoskeletal pain (3%) was identical to that reported in clinical trials in other indications.

In a small study of 24 patients, there were seven reports of treatment related splenomegaly, but in a larger study of 200 patients, there were no such reports. In the former study, no baseline measurements of spleen size were made for comparison with on-study measurements. In all cases, splenomegaly was mild or moderate on physical examination and the clinical course was benign; no patients had a diagnosis of hypersplenism and no patients underwent splenectomy. As splenic enlargement is a common finding in patients with HIV infection and is present to varying degrees in most patients with AIDS, the relationship to filgrastim treatment is unclear.

An analysis was performed on viral load data, as measured by HIV-1 RNA polymerase chain reaction (PCR), from a controlled randomised study of filgrastim for the prevention of grade 4 neutropenia. No clinically or statistically significant differences were seen between filgrastim treated groups and untreated groups for changes in viral load over a 24 week period. However, since the study was not powered to show equivalence between the groups, the possibility that filgrastim affects HIV-1 replication cannot be excluded. There was also no detrimental effect on immunological markers, which is important in a population of patients in whom a decline in CD4+ T-lymphocyte count is expected. There were no safety concerns with long-term administration of filgrastim in this setting.

Postmarketing Experience Relevant to all Indications

Cases of pulmonary haemorrhage and haemoptysis have been reported in post-marketing experience after administration of G-CSF.

Rare cases of Aortitis have been reported in post-marketing experience after administration of G-CSF.

Cases of splenomegaly have been reported commonly (≥ 1/100 and < 1/10) in patients treated with filgrastim.

Cases of splenic rupture have been reported uncommonly (≥ 1/1000 and < 1/100) in patients treated with filgrastim.

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.

DOSAGE AND ADMINISTRATION

Cancer patients receiving standard dose cytotoxic chemotherapy or induction/ consolidation chemotherapy for acute myeloid leukaemia

In adults and children receiving induction/ consolidation chemotherapy for AML, the recommended starting dose is 5 microgram/kg/day administered as a single daily subcutaneous injection.

In patients with nonmyeloid malignancies receiving standard dose cytotoxic chemotherapy, the recommended starting dose of TEVAGRASTIM is 5 microgram/kg/day, administered as a single daily subcutaneous injection or short intravenous infusion (over 15 to 30 minutes). In phase III trials efficacy was observed at doses of 4 to 8 microgram/kg/day.

TEVAGRASTIM should not be administered in the period 24 hours before to 24 hours after the administration of chemotherapy (see Precautions).

The duration of TEVAGRASTIM therapy needed to attenuate chemotherapy induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. In patients with nonmyeloid malignancies receiving standard dose cytotoxic

chemotherapy, TEVAGRASTIM should be administered daily for up to two weeks, until the ANC has reached 10 x 10^9/L following the expected chemotherapy induced neutrophil nadir. In patients with AML receiving induction or consolidation chemotherapy, TEVAGRASTIM should be administered daily until the ANC has reached > 1.0 x 10^9/L for three consecutive days or > 10 x 10^9/L for one day following the expected chemotherapy induced neutrophil nadir.

Patients with nonmyeloid malignancies receiving high dose cytotoxic chemotherapy with autologous or allogeneic bone marrow or peripheral blood progenitor cell transplantation.
The recommended starting dose of TEVAGRASTIM is 10 microgram/kg/day given by continuous subcutaneous infusion or by intravenous infusion over 4 to 24 hours. TEVAGRASTIM should be diluted in 25 to 50 mL of glucose 5% solution. The first dose of TEVAGRASTIM should be administered not less than 24 hours following cytotoxic chemotherapy and within 24 hours of bone marrow or PBPC infusion.

Once the neutrophil nadir has been passed, the daily dose of TEVAGRASTIM should be titrated against the neutrophil response as follows.

If the ANC is > 1 x 10^9/L for three consecutive days, reduce the TEVAGRASTIM dose to 5 microgram/kg/day.*

Then, if the ANC remains > 1 x 10^9/L for three consecutive days, discontinue TEVAGRASTIM. If the ANC decreases to < 1 x 10^9/L, resume TEVAGRASTIM at 5 microgram/kg/day.

*If the ANC decreases to < 1 x 10^9/L at any time during the 5 microgram/kg/day administration, TEVAGRASTIM should be increased to 10 microgram/kg/day and the above steps should then be followed.

Patients with myeloid malignancies receiving high dose cytotoxic chemotherapy with autologous or allogeneic bone marrow or peripheral blood progenitor cell transplantation.
Following transplant, the recommended dose of TEVAGRASTIM to be given to the recipient is 5 microgram/kg/day until neutrophil recovery (up to 28 days). When given after transplantation, the first dose of TEVAGRASTIM should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after infusion of bone marrow or PBPCs.

Autologous peripheral blood progenitor cell collection and therapy.
The recommended dose of TEVAGRASTIM for peripheral blood progenitor cell mobilisation when used alone is 10 microgram/kg/day given as a single daily subcutaneous injection or a continuous 24 hour infusion. TEVAGRASTIM therapy should be given for at least four days before the first leukapheresis procedure, and should be continued through to the day of the last leukapheresis procedure. Collections should be commenced on day 5 and continued on consecutive days until the desired yield of haemopoietic progenitor cells is obtained. For peripheral blood progenitor cells mobilised with TEVAGRASTIM alone, a schedule of leukapheresis collections on days 5, 6 and 7 of a seven day treatment regimen has been found to be effective. In some patients with extensive prior chemotherapy, additional daily doses of TEVAGRASTIM may be required to support additional leukaphereses to reach the desired target yield of cells (see Precautions, Peripheral blood progenitor cell collection and therapy, Prior exposure to cytotoxic agents).

The recommended dose of TEVAGRASTIM for peripheral blood progenitor cell mobilisation after myelosuppressive chemotherapy is 5 microgram/kg/day given daily by subcutaneous injection from 24 hours after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be commenced during the period when the ANC rises from $< 0.5 \times 10^9$/L to $> 5.0 \times 10^9$/L. Leukapheresis collection should be repeated on consecutive days until an adequate number of progenitor cells is obtained (see Precautions, Peripheral blood progenitor cell collection and therapy, Prior exposure to cytotoxic agents).

In all clinical trials of filgrastim for the mobilisation of peripheral blood progenitor cells, filgrastim was administered following infusion of the collected cells. In the randomised phase III study, patients received filgrastim 5 microgram/kg/day after transplantation until a sustainable ANC ($> 0.5 \times 10^9$/L) was reached (see Pharmacology, Peripheral blood progenitor cell collection and therapy). When given after transplantation, the first dose of TEVAGRASTIM should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after infusion of peripheral blood progenitor cells.

Allogeneic peripheral blood progenitor cell collection from normal donors.
For PBPC mobilisation in normal donors, TEVAGRASTIM should be administered at 10 microgram/kg/day subcutaneously for four to five consecutive days. Leukapheresis should be started on day 5 and daily collections continued on day 6 in order to collect a target yield of 4×10^6 CD34+ cells/kg recipient bodyweight.

Severe chronic neutropenia.
Diagnosis
Care should be taken to confirm the diagnosis of severe chronic neutropenia, which may be difficult to distinguish from myelodysplasia, before initiating TEVAGRASTIM therapy.
It is essential that serial full blood counts with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype be performed prior to initiation of TEVAGRASTIM therapy.

Congenital neutropenia
The recommended daily starting dose is 12 microgram/kg subcutaneously every day (single or divided doses).

Idiopathic or cyclic neutropenia
The recommended daily starting dose is 5 microgram/kg subcutaneously every day (single or divided doses).

TEVAGRASTIM may be administered subcutaneously as a single daily injection to increase and sustain the average neutrophil count above 1.5×10^9/L. Chronic daily administration is required to maintain an adequate neutrophil count. After one to two weeks of therapy, the initial dose may be doubled or halved. Subsequently, the dose may be individually adjusted not more than every one to two weeks to maintain the average neutrophil count between 1.5 and 10×10^9/L. The dose should be reduced if the ANC is persistently above 10×10^9/L for one to two weeks.

In clinical trials, 97% of patients who responded to treatment with filgrastim were treated at doses less than or equal to 24 microgram/kg/day. In the SCN postmarketing surveillance study,

the reported median daily doses of filgrastim were 6.0 microgram/kg (congenital neutropenia), 2.1 microgram/kg (cyclic neutropenia) and 1.2 microgram/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of filgrastim greater than or equal to 100 microgram/kg/day.

HIV infection

For reversal of neutropenia

The recommended starting dose of TEVAGRASTIM is 1 microgram/kg/day administered daily by subcutaneous injection with titration up to a maximum of 5 microgram/kg/day until a normal neutrophil count is reached and can be maintained (ANC greater than or equal to 2.0 x 10^9/L). In clinical studies, 96% of patients responded to filgrastim at these doses, achieving reversal of neutropenia in a median of two days.

In a small number of patients (2%), doses of up to 10 microgram/kg/day were required to achieve reversal of neutropenia.

For maintaining neutrophil counts

When reversal of neutropenia has been achieved, the minimal effective dose of TEVAGRASTIM to maintain a normal neutrophil count should be established. Initial dose adjustment to three times weekly dosing with 300 microgram/day by subcutaneous injection is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at greater than or equal to 2.0 x 10^9/L. In clinical studies, dosing with 300 microgram/day on one to seven days per week was required to maintain the ANC greater than or equal to 2.0 x 10^9/L, with the median dose frequency being three days per week. Long-term administration may be required to maintain the ANC greater than or equal to 2.0 x 10^9/L. TEVAGRASTIM dosing should be reduced and then stopped if myelosuppressive medication is discontinued and there is no recurrence of neutropenia.

Dilution and sterile transfer

TEVAGRASTIM syringes should be used in one patient on one occasion only and any residue discarded.

If required, TEVAGRASTIM may be diluted in glucose 5%. TEVAGRASTIM diluted to concentrations below 15 microgram/mL should be protected from adsorption to plastic materials by addition of albumin (human) to a final concentration of 2 mg/mL. When diluted in glucose 5% or glucose 5% plus albumin (human), TEVAGRASTIM is compatible with glass and a variety of plastics including PVC, polyolefin and polypropylene.

Dilution to a final concentration of less than filgrastim 5 microgram/mL is not recommended at any time. Do not dilute with saline at any time; product may precipitate. Infusion should be complete within 24 hours of the sterile dilution and transfer.
To reduce microbiological hazard, TEVAGRASTIM should be used as soon as practicable after dilution. If it is not administered immediately, it must be stored in the refrigerator at 2-8°Cand infusion must be complete within 24 hours of dilution.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit; if particulates or discolouration are observed, the container should not be used.

OVERDOSAGE

The maximum tolerated dose of TEVAGRASTIM has not been determined. Twenty seven patients have been treated at filgrastim doses of greater than or equal to 69 microgram/kg/day. Of those, six patients have been treated at 115 microgram/kg/day with no toxic effects attributable to filgrastim. Efficacy has been demonstrated using much lower doses. (Doses of 4 to 8 microgram/kg/day showed efficacy in the phase III study.) Doses of TEVAGRASTRIM that increase the ANC beyond 10 x 10^9/L may not result in any additional clinical benefit.

In clinical trials of filgrastim in cancer patients receiving myelosuppressive chemotherapy, white blood cell counts > 100 x 10^9/L have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects.

It is recommended, to avoid the potential risks of excessive leucocytosis, that TEVAGRASTIM therapy should be discontinued if the ANC surpasses 10 x 10^9/L after the chemotherapy induced ANC nadir has occurred.

In cancer patients receiving myelosuppressive chemotherapy, discontinuation of TEVAGRASTRIM therapy usually results in a 50% decrease in circulating neutrophils within one to two days, with a return to pretreatment levels in one to seven days.

PRESENTATION AND STORAGE CONDITIONS

TEVAGRASTIM (solution for injection or infusion) is available in strengths of 300mcg/0.5mL prefilled syringes in packs of 1's, 5's and 10's[1].

TEVAGRASTIM (solution for injection or infusion) is available in strengths of 480mcg/0.8mL prefilled syringes in packs of 1's, 5's and 10's[1].

Store between 2 to 8°C. To reduce micro biological hazard, TEVAGRASTIM should be used as soon as practicable after dilution. If it is not administered immediately, it must be stored in the refrigerator at 2°C to 8°C and infusion must be complete within 24 hours of dilution.

NAME AND ADDRESS OF SPONSOR

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37 Epping Rd
Macquarie Park
NSW 2113
Telephone: 1800 288 382

[1] Note: Not all pack sizes may be marketed.

POISONS SCHEDULE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

29 August 2011

DATE OF MOST RECENT AMENDMENT

28 November 2018