SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Grafalon®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of the concentrate contains 20 mg anti-human T-lymphocyte immunoglobulin from rabbits.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent and colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis and therapy of rejection crisis in organ and tissue transplantations.

Prevention of graft-versus-host disease (GVHD) in adults after allogeneic stem cell transplantation (SCT)
Grafalon is indicated for prevention of graft-versus-host disease (GVHD) in adults with haematological malignancies following stem cell transplantation from matched unrelated donors in combination with standard Cyclosporin A/methotrexate prophylaxis.

4.2 Posology and method of administration

Grafalon should be prescribed only by physicians who are experienced in the use of immunosuppressive therapies. Grafalon must be administered under qualified medical supervision.

Posology
The dose of Grafalon is dependent on the indication. Dose recommendations are based on body weight (BW).

Prevention of acute transplant rejection in patients receiving allogeneic solid organ transplants
The recommended dose range is 2 to 5 mg/kg BW/d Grafalon. The most common doses are in the range of 3 to 4 mg/kg BW/d. Therapy should commence on the day of transplantation pre-, intra-, or immediately post-operatively. Depending on the patient's condition, selected daily dose and the concomitant immunosuppressive regimen, the recommended duration of therapy is in the range of 5 to 14 days.

Therapy of acute corticosteroid-resistant rejection after allogeneic solid organ transplantation
The recommended dose range is 3 to 5 mg/kg BW/d Grafalon. The most common dosages are in the range of 3 to 4 mg/kg BW/d. Duration of therapy will vary according to the condition of the grafted organ and clinical response, usually between 5 to 14 days.

Prevention of graft-versus-host disease (GVHD) in adults after allogeneic stem cell transplantation (SCT)
As part of myeloablative conditioning regimens for stem cell transplantation, the recommended dose is 20 mg/kg BW/d of Grafalon, usually starting from day -3 to day -1 prior to SCT.

Method of administration
Intravenous use (after dilution)
Grafalon is a hypotonic concentrate for solution for infusion with pH 3.7 ± 0.3 and is not for direct injection. It has to be diluted in sodium chloride 9 mg/ml (0.9%) solution before intravenous administration to the patient. A dilution ratio of 1:7 is recommended (per 1 ml Grafalon 6 ml sodium chloride solution should be added) to maintain the required level of osmolality. Higher dilution ratios, with attendant higher pH levels of the infusion solution, may result in particle formation. Solutions containing visible particles must not be used.

The standard infusion time in organ transplantation is 4 hours while in stem cell transplantation, 4 to 12 hours infusion times are recommended. In case of intra-operative administration, infusion time of 0.5 to 2 hours has been usually used.

During administration, the patient shall be closely monitored for symptoms of hypersensitivity or anaphylaxis. The first dose of Grafalon should be administered at a reduced infusion rate for the first 30 minutes. If no symptoms of intolerance occur, the infusion rate may be increased. In case of anaphylactic or anaphylactoid reactions, the responsible physician must be prepared to deal promptly with such an event and appropriate medical treatment has to be implemented.

Alternatively to infusion via central venous catheter, a peripheral vein with high flow rate and large diameter can be chosen. The administration of methylprednisolone and/or antihistamines prior to infusion is recommended in order to improve systemic and local tolerance. Apart from standard hygienic precautions at the injection site, reduction of the infusion speed and/or change of the venous access site are to be considered.

Sodium heparin must not be added to the Grafalon infusion solution or administered via the same infusion set, see section 6.2.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Grafalon is contraindicated in patients with bacterial, viral, parasitic or mycotic infections which are not under adequate therapeutic control.

Grafalon is contraindicated in solid organ transplant patients with severe thrombocytopenia, i.e. less than 50,000 platelets/µl because Grafalon may enhance thrombocytopenia and thus increase the risk of hemorrhage.

Grafalon is contraindicated in patients with malignant tumours except in cases where stem cell transplantation is performed as part of the treatment.

4.4 Special warnings and precautions for use

Patients receiving Grafalon must be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources to provide emergency treatment if necessary. Grafalon must be administered and monitored under appropriately qualified medical supervision.

Hypersensitivity reactions
Hypersensitivity reactions have been reported with the administration of Grafalon.
Before the first administration of Grafalon, it is recommended to determine whether the patient has an anamnestical allergic predisposition, in particular to rabbit proteins.
In case of re-exposure in form of re-therapy with Grafalon or treatment with rabbit immunoglobulin preparations of other manufacturers, the risk of developing an anaphylactic reaction is increased due to a possible sensitisation during the former therapy.

Severe thrombocytopenia
Treatment with Grafalon should be interrupted or stopped in solid organ transplant patients in whom severe thrombocytopenia develops (i.e. less than 50,000 platelets/µl) as Grafalon may enhance thrombocytopenia and thus increase the risk of hemorrhage. Clinical personnel should be prepared for appropriate emergency measures.

Hepatic disorders
Grafalon has to be administered with special caution in patients with hepatic diseases as it may aggravate pre-existing clotting disorders. Careful monitoring of thrombocytes and coagulation parameters is recommended.

Cardiovascular disorders
Grafalon has to be administered with special caution in patients with known or suspected cardiovascular disorders. In patients with hypotension or cardiac decompensation with orthostatic symptoms (e.g. unconsciousness, weakness, vomiting, nausea), slowing/interrupting the infusion should be considered.

Infections
Immunosuppressive therapy increases the risk for infections in general. Grafalon treated patients have an increased risk for the development of bacterial, viral, parasitic, and/or mycotic infections. Adequate monitoring and treatment measures are indicated. In patients undergoing stem cell transplantation, monitoring of CMV- and EBV-status and adequate pre-emptive therapy are recommended.

Vaccination
During treatment with Grafalon, patients should be advised that non-live vaccinations might be less efficacious. Live attenuated virus vaccination is contraindicated in immunosuppressed patients.

Warning on transmissible agents
Standard measures to prevent infections resulting from the use of medicinal products prepared by using human components include careful selection of donors, screening of individual donations for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared by using human components are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken for Grafalon are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A and parvovirus B19 viruses.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Immunosuppressive medicinal products
In addition to Grafalon, other concomitant immunosuppressive medicinal products are routinely administered. No direct interaction between Grafalon and corticosteroids, purine antagonists, calcineurin inhibitors or mTOR inhibitors has been observed. However, the co-administration of these medicinal products may increase the risk of infection, thrombocytopenia, and anemia. Thus, patients receiving combined immunosuppressive therapies are to be monitored carefully and an adequate adaptation of the regimen is recommended.

Vaccination
For immunosuppressed patients live attenuated virus vaccination is contraindicated. The antibody response to other vaccines may be diminished (see section 4.4).

4.6 Fertility, pregnancy and lactation

No animal data are available. Clinical data on pregnant or breast-feeding women are not available either.

Pregnancy
The potential risk for the fetus is unknown. Caution should be exercised when prescribing to pregnant women.

Breastfeeding
At least human immunoglobulin can potentially penetrate the placental barrier or be excreted into human breast milk. Therefore, the decision to treat pregnant or lactating women should be made by the treating physician and based on a risk/benefit evaluation.

Fertility
No data on fertility are available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile
Grafalon is an immunoglobulin product with immunosuppressive properties. Well-known class-related adverse effects include cytokine-release related symptoms, hypersensitivity reactions such as anaphylaxis and other allergic phenomena, enhanced susceptibility to infections, and occurrence of malignancies.

The nature and frequency of adverse reactions described in this section were analysed in an integrated safety analysis on the basis of 6 clinical studies consisting of 242 patients in the indications prevention of rejection in patients receiving renal transplants (136 patients) and conditioning prior to allogeneic stem cell transplantation (106 patients). Approx. 94% of the patients analysed experienced at least one adverse reaction. The pattern of adverse reactions reflects in part common complications typically occurring after the respective procedures - renal transplantation (urinary tract infection, renal failure) and stem cell transplantation (pancytopenia, mucosal inflammation).

In the table below, adverse reactions reported with Grafalon are listed and classified according to frequency and System Organ Class. Frequency groupings are defined according to the following convention:
very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Infections and infestations	
Very common	CMV infection*, urinary tract infection*
Common	bacterial sepsis**, pneumonia**, pyelonephritis*, herpes infection, influenza, oral candidiasis, bronchitis, rhinitis, sinusitis, nasopharyngitis, skin infection
Uncommon	catheter site infection, Epstein-Barr virus infection, gastrointestinal infection, erysipelas, wound infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Common	lymphoproliferative disorder*
Blood and lymphatic system disorders	
Very common	anemia
Common	pancytopenia**, thrombocytopenia, leukopenia
Uncommon	polycythemia
Immune system disorders	
Common	anaphylactic shock**, anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders	
Common	hyperlipidemia
Uncommon	fluid retention, hypercholesterolemia
Nervous system disorders	
Very common	headache, tremor
Common	paresthesia
Eye disorders	
Common	photophobia
Cardiac disorders	
Common	tachycardia
Vascular disorders	
Very common	flushing
Common	hypotension*, venoocclusive disease, hypertension
Uncommon	shock**, lymphocele
Respiratory, thoracic and mediastinal disorders	
Very common	dyspnea
Common	cough, epistaxis
Gastrointestinal disorders	
Very common	vomiting, nausea, diarrhea, abdominal pain
Common	stomatitis
Uncommon	reflux esophagitis, dyspepsia
Hepatobiliary disorders	
Common	hyperbilirubinemia
Skin and subcutaneous tissue disorders	
Common	erythema, pruritus, rash
Uncommon	drug eruption
Musculoskeletal and connective tissue disorders	
Common	myalgia, arthralgia, back pain, musculoskeletal stiffness
Renal and urinary disorders	
Common	renal tubular necrosis*, hematuria
Uncommon	renal failure**, renal necrosis*
General disorders and administration site conditions	
Very common	pyrexia**, chills
Common	asthenia, chest pain, hyperthermia, mucosal inflammation, peripheral edema
Uncommon	edema
Investigations	
Common	blood creatinine increased*, Cytomegalovirus antigen positive, C-reactive protein increased
Uncommon	hepatic enzymes increased

* serious reaction
** serious reaction, in single cases with fatal outcome

Description of selected adverse reactions

Cytokine release related symptoms

These reactions occur due to release of cytokines and include fever, chills, headache, nausea, vomiting, tachycardia, and circulatory changes. These reactions could be summarized under the clinical entity of cytokine release syndrome. They are frequently observed during or after the administration of Grafalon. Symptoms are usually well manageable. Prophylactic medication could be administered to alleviate these symptoms.

Hypersensitivity reactions

Reactions such as flushing, rash, erythema, edema, dyspnea with or without bronchospasm, and cough are commonly observed during and after the administration. These reactions usually respond to treatment well. The administration of appropriate prophylactic medication can ameliorate these symptoms. The occurrence of anaphylaxis/anaphylactic shock requires immediate termination of the infusion. Serum sickness, observed when Grafalon is administered for long treatment duration and at lower dosage, is rarely severe and usually responds well to symptomatic treatment.

Hematological changes

Transient changes of thrombocyte and leukocyte counts, also known as thrombocytopenia and leukopenia are commonly observed after Grafalon administration. Anemia is also very commonly observed after administration of Grafalon.

Infections

The patients treated with immunosuppressive regimens have an increased susceptibility to infections. In the first year after solid organ transplantation, the majority of patients who received Grafalon developed infections of bacterial, viral or mycotic origin. Urinary tract infection is a very common bacterial infection; very common viral infections are caused by cytomegalovirus (CMV). Commonly reported infections include bacterial sepsis, bacterial pneumonia, pyelonephritis, herpetic viral infections, and oral candidiasis. EBV infections, CMV pneumonia and CMV gastroenteritis are uncommon viral infections. Systemic candidiasis is an uncommon fungal infection. The majority of infections are usually manageable with the respective treatment. There were isolated reports of life-threatening or even fatal infections. Appropriate monitoring and prophylactic treatment can reduce the infection rate.

Malignancy

The incidence of malignancy occurring after Grafalon treatment is generally low across studies and publications and is comparable with the incidence observed with other combinations of immunosuppressive medications. Post-transplant lymphoproliferative disease was reported exclusively from patients who underwent allogeneic stem cell transplantation (1.7%).

Hemolysis

Rare cases (less than 1 in every 1000 patients) of hemolysis were reported in connection with Grafalon administration and were fatal in isolated cases.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

In case of overdose, immediate use of broad-spectrum antibiotics, antimycotic and antiviral therapy is recommended. Grafalon therapy must be discontinued and any other concurrent immunosuppressive treatment must be adjusted according to the hemogram (in particular, leukocytes and lymphocytes). The platelet count must be monitored closely and substitution therapy initiated as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: specific immunosuppressant, ATC code: L04AA04.

Grafalon is a polyclonal anti-human-T-lymphocyte immunoglobulin derived from rabbits immunized with Jurkat cells, a human lymphoblastoid cell line. The expression of T-cell markers on Jurkat cells is consistent with the effects of Grafalon on lymphocytes. Grafalon has been found to contain antibodies against further surface antigens of Jurkat cells.

Analysis of lymphocyte subsets in patients who received Grafalon, showed a decrease in lymphocyte subsets carrying surface proteins, which are expressed by the Jurkat cell line.
Grafalon is cytotoxic against human lymphocytes. Available data show that activated lymphocytes are more susceptible.

Grafalon did not activate T-cells (via CD3) or lymphocytes but inhibited activation of T-cells by an anti-CD3 antibody.

Grafalon reduced migration of human melanoma cells by binding to adhesion molecules.

Anti-adhesive properties (anti-LFA-1 and anti-ICAM-1 activity) might explain why addition of Grafalon diminished the vascular resistance of kidney vessels and reduced lymphocyte retention in the kidney when porcine kidneys were perfused with human lymphocytes incubated with or without Grafalon.

Grafalon prolonged skin graft survival in rhesus monkeys. Immunosuppression was evident in this model and leukopenia and lymphopenia were observed. In cynomolgus monkeys, Grafalon had a beneficial effect on ischemia/reperfusion injury by inhibition of adhesion of lymphocytes and neutrophils.

In renal transplant patients under standard therapy with Grafalon, leukocyte, and platelet counts decreased but returned to normal levels within 10 days after transplantation. Also counts of lymphocytes and lymphocyte subpopulations decreased significantly. A decrease in CD2, CD3, CD4 and CD8 count was observed. A return to levels within normal range was seen for CD8 but not for CD2, CD3 and CD4 in the first 20 post-operative days.

The described effect of standard therapy with Grafalon on lymphocyte subpopulations and a persistent reversal of the CD4/CD8 ratio for up to 66 months were reported in patients after kidney transplantation.

After a single high-dose of 9 mg/kg BW Grafalon, TNF-α and IL-10 increased, while IL-12p40 slightly decreased and IL-12p70 was not stimulated.

Stem cell transplantation study
Results of a 2-year follow-up stem cell transplantation study with matched unrelated donor grafts showed that the incidence of acute graft-versus-host disease (aGVHD), chronic GVHD (cGVHD) and mortality due to GVHD was decreased in patients receiving Grafalon in addition to standard prophylaxis compared to patients receiving only GVHD standard prophylaxis.

Methods:
The study was a Phase 3 prospective, open-label randomised, multicentre study conducted in 10 countries at 31 centres across Europe, enrolling 202 adult patients with haematological malignancies.
One group (98 patients) received standard prophylaxis with cyclosporin and methotrexate, whilst the other group (103 patients) received Grafalon in addition to standard prophylaxis; 20 mg/kg of Grafalon was administered on Day -3, Day -2 and Day -1 prior to SCT. 201 patients who underwent transplantation with peripheral blood (n = 164; 82%) or bone marrow (n = 37; 18%) grafts from matched unrelated donors after myeloablative conditioning were included in the study. The primary endpoint was early treatment failure: Severe aGVHD grade III - IV or death within 100 days of transplantation.

Results:
The addition of Grafalon to standard prophylaxis resulted in a decreased incidence of all forms of GVHD: aGVHD (severity groups I - IV, II - IV and III - IV) and cGVHD (limited and extensive form). There were no differences between treatment groups with regard to relapse, transplant-related mortality, and overall survival.

Primary endpoint: The incidence of early treatment failure was 21.4%, compared to 34.7% in the control group (adjusted odds ratio 0.56, CI [0.28 - 1.11]; p = 0.0983). The cumulative incidence of aGVHD grade III - IV was 11.7% in the Grafalon group versus 25.5% in the control group (adjusted hazard ratio [HR] 0.48, CI [0.24 - 0.96]; p = 0.0392). The cumulative incidence of aGVHD grade II - IV was 33.0% in the Grafalon group versus 52.0% in the control group (adjusted HR 0.55, CI [0.35 - 0.85]; p = 0.0077).

The 2-year post-transplantation follow-up incidence of extensive chronic GVHD with Grafalon was 12.2% versus 45.0% in the control group without Grafalon prophylaxis (adjusted HR 0.196, CI [0.10 - 0.39]; p < 0.0001).

Figure 1 Relative Risk of Grafalon prophylaxis vs. control group without Grafalon prophylaxis for primary and secondary efficacy parameters (point estimator and 95% CI)

5.2 Pharmacokinetic properties

Grafalon is administered intravenously and is therefore 100% bioavailable.

Grafalon is subject to protein metabolism as are other bodily proteins.

The half-life of Grafalon is approximately 14 days (in case of a dosage of 4 mg/kg BW/d over 7 days) and varies from 4 to 45 days depending on the dose and duration of administration.

Literature studies have shown that T-cell specific antibodies were eliminated faster than total rabbit IgG.

Pharmacokinetic data have been obtained from the toxicokinetic sections of the toxicology studies. Grafalon is absorbed rapidly and is eliminated slowly. Systemic exposure was proportionate at all dose levels, increased with repeated dosing, without gender differences. No drug-drug interactions with prednisolone were seen.

5.3 Preclinical safety data

In non-clinical toxicology studies Grafalon was investigated in single dose studies in rabbits, cynomolgus monkeys and rhesus monkeys, and in repeat-dose studies in rhesus monkeys. Grafalon was well tolerated. Some of the effects observed are due to the specific pharmacodynamic activity of Grafalon, which results in immunosuppression and pronounced decrease in lymphocyte count, particularly T-lymphocytes. At high doses (250 to 300 mg/kg BW), anaphylactic reactions have been observed in rhesus monkeys. Co-administration of prednisolone reduced the toxicity of Grafalon. No serum sickness was observed and there was a marked improvement in the clinical signs compared to the administration of Grafalon alone.

No effects on the CNS, cardiovascular or respiratory systems were observed in a safety pharmacology study in cats.

No genotoxic activity, no local irritation and no anti-glomerular basement membrane antibodies were observed. Carcinogenicity or reproductive toxicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate
Phosphoric acid (85%) (for pH adjustment)
Water for injections

6.2 Incompatibilities

Grafalon concentrate for solution for infusion must not be mixed with glucose, blood, blood-derivatives, solutions containing lipids, and sodium heparin.
Siliconised syringes must not be used for the withdrawal of Grafalon from the vials or for the preparation of the infusion solution.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at room temperature. However, from a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are at the responsibility of the user.
Not intended for multiple withdrawals.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C). Keep the vial in the outer carton in order to protect from light.

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

For instruction on preparation and administration of the ready-to-use diluted infusion solution, see section 4.2.

6.5 Nature and contents of container

Pack with 1 or 10 vials	containing 5 ml solution
Pack with 1 or 10 vials	containing 10 ml solution

6.6 Special precaution for disposal

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

7. MANUFACTURER

Neovii Biotech GmbH
Am Haag 6 – 7, 82166 Grafelfing, Germany

8. REGISTRATION HOLDER

Cure Medical & Technical Supply
6 Hashiloach st., POB 3340, Petach – Tikva

9. REGISTRATION NUMBER

060-25-27341-00

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Grafalon conc for sol for inf SPC vr 01A